Upsher-Smith Laboratories, Inc.
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Clinical Research Protocol

Protocol Title:	An Open-Label Safety Study of USL261 in the Outpatient Treatment of Subjects with Seizure Clusters
Protocol Number:	P261-402
EudraCT Number:	2011-004109-25
Protocol Version:	Fifth Issue, Amendment 4 Amendment is only applicable to the United States
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Clinical Phase:	Phase III
US IND Number:	77,421

SYNOPSIS

Sponsor: Upsher-Smith Laboratories, Inc. (USL)

Name of Development Product: USL261 (intranasal midazolam)

Study Title: An Open-Label Safety Study of USL261 in the Outpatient Treatment of Subjects with Seizure Clusters

Study Number: P261-402

Study Phase: III

Study Objective(s):

To evaluate the long-term safety and tolerability of USL261 in the treatment of seizure clusters using the following assessments:

1. Caregiver-recorded respiration rate at 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours and 4 hours after study drug administration.
2. Adverse events (AEs).
3. Clinical laboratory tests.
4. Physical, nasal and neurological examinations.
5. Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiration rate, and temperature) as recorded by the study center personnel.
6. Brief Smell Identification Test (B-SIT)
7. Columbia-Suicide Severity Rating Scale (C-SSRS).
8. Requirement for unscheduled emergency room (ER) or emergency medical service (EMS) visits within 24 hours after study drug administration.

Study Design:

This is an open-label, multicenter, safety extension study of USL261 in subjects with seizure clusters who have completed study P261-401 (ARTEMIS-1). However, if study P261-401 is terminated, subjects who have completed the Test Dose Visit (Visit 2) of study P261-401 will also be eligible to enter this study (P261-402). Each seizure cluster episode will be treated with a single dose of 5.0 mg USL261. A second dose of 5.0 mg USL261 may be given if the seizure cluster has not terminated within 10 minutes after initial study drug administration or if another seizure occurs between 10 minutes and 6 hours after administration of the study drug. However, the second dose will not be administered if the subject has a respiratory rate < 8 breaths per minute, requires emergency rescue treatment with assisted breathing or intubation, or has excessive, uncharacteristic sedation (as defined by the investigator in the Patient Management Plan). After each USL261-treated seizure cluster episode, the caregiver will call the study center as soon as possible, but no later than 24 hours after USL261administration.

After obtaining informed consent and determining that the subject meets the eligibility requirements for this study, the subject/caregiver will be provided with enough study drug to treat one seizure cluster episode (1 treatment kit containing two 5.0 mg doses of USL261) at Visit 1. After one USL261-treated seizure cluster, the subject and caregiver will return to the study center for Visit 2 within 120 hours (5 days) of USL261 administration. At Visit 2, the subject/caregiver will again be provided with enough study drug to treat 1 seizure cluster episode (1 treatment kit containing two 5.0 mg doses of USL261). After one USL261-treated seizure cluster, the subject and caregiver will return to the study center for Visit 3 within 120 hours (5 days) of USL261 administration. At Visit 3 and all subsequent visits (except for the Final Visit or Early Termination Visit) the subject/caregiver will be provided with enough study drug to treat 2 seizure cluster episodes (2 treatment kits, each containing two 5.0 mg doses of USL261).

After Visit 3, subjects and caregivers will return to the study center after every second USL261-treated seizure cluster episode. Each of these visits will occur within 120 hours (5 days) after the last USL261 administration.

The duration of each subject's participation will be up to approximately 4 years from the date of enrollment (Visit 1). After this period, the study duration may be extended until marketing approval or a time period as approved by the Heath Authority where the study is being conducted. A minimum of 3 days (72 hours) is required between treatments (1 treatment is defined as the use of one or two 5.0 mg doses of USL261 from one study drug treatment kit to treat a single seizure cluster episode). There is no

limitation on the total number of seizure cluster episodes treated during the subject's participation in the study.

Before any subject is enrolled in this open-label extension study, he/she must have completed study P261-401, or, if Study P261-401 has been terminated, subjects must have completed the Test Dose Visit (Visit 2) of study P261-401. Subjects must meet all other eligibility criteria for this study. Since enrollment is limited to subjects who have participated in study P261-401, a maximum of 240 subjects (the planned number of subjects completing the Comparative Phase in P261-401) are expected to enroll.

Inclusion/Exclusion Criteria:

Inclusion

1. Subject or subject's legally acceptable representative (LAR) has provided written informed consent, and subject has provided written assent where required by local law or Institutional Review Board (IRB) / Independent Ethics Committee (IEC) policy.
2. Subject has a competent, adult (age ≥ 18 years) caregiver(s) who is able to recognize and observe the subject's seizure cluster episodes, who is willing to be trained in the study procedures, and has provided written informed consent; the caregiver(s) must be a relative, partner, friend, or LAR of the subject, or a person who provides daily care to the subject who has a significant personal relationship with the subject.
3. Subject is 12 years of age or older at Visit 1.
4. Subject has an established diagnosis of partial or generalized epilepsy.
5. Subject has a documented history of seizure clusters that includes all the following:
    a. The subject's seizure cluster pattern is observable, stereotyped, and recognizably different from the subject's other non-cluster seizure activity (if any) in seizure type, duration, severity, or frequency, and of the same type that was approved by the central reviewer in study P261-401.
    b. A documented history of seizure clusters lasting a minimum of 10 minutes from the time the seizure cluster is recognized.
    c. As part of the subject's stereotyped seizure cluster pattern, a second seizure typically occurs within 6 hours from the time of recognition of the seizure cluster.
    d. The subject's stereotyped seizure cluster pattern is composed of multiple (≥ 2) partial or generalized seizures.
    e. The subject's stereotyped seizure cluster pattern was established > 3 months before Visit 1 of study P261-401.
    f. A frequency of ≥ 3 stereotyped seizure clusters during the year before Visit 1 of study P261-401.
    g. At least 1 stereotyped seizure cluster occurring at least once in the 4 months before Visit 1 of study P261-401.
6. Subject has successfully completed study P261-401 and the subject and caregiver have demonstrated adequate compliance with P261-401 study procedures as determined by the investigator, OR, if Study P261-401 has been terminated, the subject completed the Test Dose Visit (Visit 2) of study P261-401 and the subject did not meet any Visit 2 exclusion criteria in study P261-401.
7. Subject is not likely to conceive, as indicated by a "yes" answer to at least 1 of the following questions:
    a. Is the subject a male?
    b. Is the subject a postmenopausal female as determined in study P261-401?
    c. Is the subject a female who has written medical documentation of being permanently sterilized (e.g. hysterectomy, double oophorectomy, bilateral salpingectomy)?
    d. Has the subject agreed to use two effective methods of contraception during the entire study if she is sexually active or will become sexually active during the study (except where local law or regulation differs; approval by USL or designee is required in such cases)?

    Examples of two effective methods of contraception include the following:
    - A diaphragm and a condom with spermicide.
    - An intrauterine device (IUD) used in combination with a barrier method (e.g.

condom, diaphragm, or cervical cap with spermicide).
- Hormonal methods (e.g., high-dose birth control pills, Depo-Provera) or tubal ligation used in combination with a barrier method (e.g., condom, diaphragm, or cervical cap with spermicide).

Note that hormonal contraception alone is not considered adequate for this study and must be used in combination with another method. The type of birth control used must be approved by the investigator or designee.

Exclusion

1. Subject experienced a seizure cluster progressing to status epilepticus during or since his/her participation in Study P261-401.
2. Subject has a positive pregnancy test at any visit or is pregnant, considering becoming pregnant, or is breastfeeding (female subjects only).
3. Subject who, in the opinion of the investigator, is experiencing an ongoing, uncontrolled, clinically significant adverse event(s) from P261-401 at Visit 1 or did experience a clinically significant adverse event in study P261-401 that might prevent the subject from safely participating in the study.
4. Subject has consumed any clinically significant CYP450 3A inhibitor/inducer, opioid, or other respiratory depressant, not including antiepileptic drugs (AEDs), within the required washout period before Visit 1 (see Appendix 1, Prohibited Concomitant Substances).
5. Subjects using chronic benzodiazepine(s); chronic use is defined as use for 4 or more days in a 7-day period on average.
6. Subject has a neurological disorder that is likely to progress in the next year.
7. Subject has a history of acute narrow-angle glaucoma.
8. Subject has a medical condition including uncontrolled cardiac, pulmonary, renal, hepatic, or gastrointestinal disease that could interfere with the study, subject safety/safety monitoring, or is not stable despite current therapy.
9. Subject has severe chronic cardio-respiratory disease with baseline room air oxygen saturations < 90%, New York Heart Association class III or IV functional status, or the need for ambulatory oxygen.
10. Subject has had psychogenic, non-epileptic seizure(s) during or since the P261-401 study.
11. Subject has suicidality, defined as any of the following: a) active suicidal plan/intent or active suicidal thoughts during or since the P261-401 study as defined by a Columbia-Suicide Severity Rating Scale (C-SSRS) suicidal ideation score ≥ 3, b) any suicide attempt during or since the P261-401 study as determined by the C-SSRS or medical history, or c) other clinically significant suicidality as determined by the investigator.
12. Subject, in the investigator's opinion, has met the criteria for a major depressive episode during or since the P261-401 study (criteria defined by the current edition of the Diagnostic and Statistical Manual of Mental Disorders).
13. Subject has or has had psychosis during or since the P261-401 study, excluding postictal psychosis
14. Subject has a history of drug or alcohol abuse during or since study P261-401.
15. Subject has a history of allergy or any significant adverse reaction (including rash) to midazolam
16. Subject is currently using an investigational drug or device or has used such (other than the study drug during P261-401) within 30 days prior to Visit 1.
17. Subject has plasma phenobarbital concentrations > 35 µg/mL at Visit 1 (phenobarbital concentration will be measured in subjects taking phenobarbital and in subjects for which the investigator deems it necessary).
18. Subject is not appropriate for the study for any other reason as determined by the investigator.

Study Population: Since enrollment is limited to subjects who have participated in study P261-401, a maximum of 240 subjects (the planned number of subjects completing the Comparative Phase in P261-401) is expected to enroll.

Test/Reference Product, Dose, and Mode of Administration:
Test Product: USL261 (intranasal midazolam); 5.0 mg per actuation for intranasal administration.
Reference Product: None

Duration of Treatment: Each seizure cluster episode will be treated with one 5.0-mg dose of USL261 followed by a second 5.0-mg dose of USL261 if the seizure(s) has not terminated within 10 minutes after study drug administration or if another seizure occurs between 10 minutes and 6 hours after administration of the drug and the subject does not have excessive, uncharacteristic sedation (as defined by the investigator in the Patient Management Plan), does not have a respiratory rate < 8 breaths per minute, and does not require emergency rescue treatment with assisted breathing or intubation. There must be at least 3 days (72 hours) between treatments. There will be no limitation on the total number of seizure cluster episodes treated.

Duration of Subject Participation:
Screening: Up to 28 days for transition from P261-401 protocol.
Treatment Phase: The duration of each subject's participation will be variable. If the subject continues to be eligible, s/he can continue in the study for up to approximately 4 years from the date of enrollment (Visit 1). After this period, the study duration may be extended until marketing approval or a time period as approved by the Heath Authority where the study is being conducted or until a time determined by the Sponsor (Upsher-Smith Laboratories, Inc.)

Safety Assessments:
Collection of AEs, physical, nasal and neurological examinations, clinical laboratory evaluations, vital sign measurements, caregiver-recorded respiration rate, C-SSRS, ER or EMS visits, and B-SIT.

Efficacy Assessments:
- Date and time of study drug administration.
- Seizure activity:
  - For the first 2 years of participation in the study the date, start, and stop time of each seizure within 24 hours after any study drug administration.
  - After the first 2 years participation in the study the date and start time of next seizure within 10 minutes to 24 hours after administration of the first and second dose of study drug.

Statistical Methods:
All analyses will be descriptive and no hypothesis tests will be conducted. Data will be listed and tabulated overall. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Categorical data will be presented using counts and percentages.

The Safety Population includes all subjects who are enrolled in the open-label study and received at least one dose of open-label study drug. The Efficacy Evaluable Population includes all subjects in the Safety Population who received at least 1 dose of study drug during the open-label study and who have any post-treatment efficacy assessment.

The following safety endpoints will be summarized using the Safety Population:
- Treatment Emergent Adverse Events (TEAEs) will be presented by treatment received, severity, relationship to study drug and age group (< 18, ≥ 18 - <65 years, ≥65 years).
- Clinical laboratory results will be presented by visit.
- Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiration rate, and temperature) performed by study center staff will be summarized at each visit.
- Caregiver-recorded respiration rate will be presented using descriptive statistics at each time point and for each treatment. The number of subjects who have < 8 breaths per minute and > 24 breaths per minute after study drug administration will be presented by time point and for each treatment.
- Number of subjects requiring an unscheduled ER or EMS visit within 24 hours after study drug administration will be presented for each treatment.
- Suicidal behavior and ideation using the C-SSRS will be summarized at each visit.
- Physical, nasal and neurological examination results will be presented by visit.

- Olfactory assessment results will be presented by treatment group and visit

The following efficacy endpoints will be summarized using the Efficacy Evaluable Population:

- Short and long term efficacy of USL261 as the outpatient treatment of seizure clusters based on Treatment Success based on appropriate longitudinal model
- Kaplan-Meier analysis of time to return to baseline functionality

The following questionnaires will be summarized using the Safety Population:

- SF-12v2 Health Survey (SF-12v2).
- Treatment Satisfaction Questionnaire for Medication (TSQM).
- Intranasal Therapy Impact Questionnaire (ITIQ).
- Caregiver Questionnaire.

Table 1. Procedure Schedule

Phase	Screening	Treatment Phase			Study Termination
Visit Number	**Visit 1[a]**	**Visits 2 and 3 [b]**	**Visit X [c]**	**Treatment [d]**	**Final Visit or Early Termination**
Study Assessment					
Obtain Informed Consent[e]	X				
Contact IRT System	X	X	X		X
Confirm Inclusion/Exclusion Criteria	X				
Caregiver training[f]	X	X	X		
Medical / Surgical / Medication History[g]	X				
Concomitant therapy review[g]	X	X	X		X
ER and EMS Visit Review [h]		X	X		X
Update PMP[i]	X				
Physical Examination	X[j]	X	X		X
Neurological Examination	X[j,k]	X[l]	X[l]		X[k]
Nasal Examination	X[j]	X	X		X
B-SIT		X	X		X
Pregnancy Test – Urine[m]	X	X	X		X
Clinical Laboratory Testing[n]	X	X	X		X
Height	X				X
Body weight	X	X	X		X
Vital Sign measurements[o]	X	X	X		X
Study drug administration				X	
Caregiver call to study center				X	
Record seizure activity for 24 hours after study drug administration in the subject workbook				X[p]	
Evaluate subject's return to baseline functionality[q]				X	
Caregiver-recorded respiration rate[r]				X	
C-SSRS[s]	X	X	X		X
Outcome questionnaires[t]	X	X	X		X
Dispense Study Materials Kit[u]	X[v]				
Study Drug Kit [v]		X	X		
Drug Accountability		X	X		X
Collect and review Subject Workbook		X	X		X
AE Assessment	X	X	X	X	X

Telephone Follow-Up [w]		Approximately every 30 days (between visits that are at least 30 days apart)

[a] Procedures at Visit 1 may occur at the same time as Visit 4 of the preceding double-blind study (P261-401) or up to 28 days after Visit 4 of study P261-401. If Visit 1 of this study (P261-402) is on the same day as Visit 4 of study P261-401, the procedures performed at Visit 4 of study P261-401 that are common to Visit 1 will be used for both studies. If Visit 1 for this study (P261-402) is not on the same day as Visit 4 of P261-401, all necessary procedures will be repeated, except for physical exam, neurological exam, nasal exam, and clinical laboratory testing (hematology, serum chemistry and urinalysis).
[b] Visits 2 and 3 will take place within 120 hours (5 days) following each of the first 2 USL261-treated seizure cluster episodes.
[c] After Visit 3, each subject will return to the study center for a visit after every second USL261-treated episode. There is no limit on the number of seizure cluster episodes treated.
[d] These assessments are to be completed by the caregiver(s) outside of the study center.
[e] Informed consent provided by the subject (or subject's LAR) and caregiver before any other study-specific procedures; assent may also be required for some subjects and subjects with LARs (see Section 5.4, Informed Consent).
[f] Caregiver training for P261-402 is required before study drug is dispensed at Visit 1. Review and re-instruct subjects and caregivers on the information provided in the training at all subsequent visits, except Final Visit or Early Termination Visit. Caregivers are also required to have a current CPR training certificate throughout the entire study.
[g] Update from Study P261-401.
[h] Collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since last visit or follow-up phone call
[i] PMP from P261-401 will be updated for this study (see Section 9.3.1). PMP updates should be completed before a subject receives the study materials kit at Visit 1.
[j] The physical, nasal, and neurological examinations performed at Visit 4 of Study P261-401 will be used for Visit 1 of this study.
[k] Complete neurological examination.
[l] Brief neurological examination.
[m] Pregnancy tests required only for females of childbearing potential as described in Section 6.2.2.4.
[n]Hematology, serum chemistry, and urinalysis for all subjects; phenobarbital screen/levels for subjects taking phenobarbital and in subjects for which the investigator deems it necessary.
[o] Blood pressure (BP), heart rate (HR), respiration rate, and body temperature.
[p] For the first 2 years of participation in the study the date, start, and stop time of each seizure within 24 hours after any study drug administration will be recorded. After the first 2 years participation in the study, the date and start time of next seizure within 10 minutes to 24 hours after administration of the first and second dose of study drug will be recorded.
[q] Caregiver will evaluate the subject's return to baseline functionality after each treated seizure cluster episode and record the time when the subject was able to return to what he/she was doing.
[r]Caregiver counts the number of breaths taken by the subject during a 30-second interval. Caregivers will measure respiration rate at approximately 10, 15 and 30 minutes and 1, 2, and 4 hours after USL261 administration (see Section 6.1.3).
[s] The Since Last Visit version is administered at all visits.
[t] The outcome questionnaires SF-12v2, TSQM, ITIQ and Caregiver Questionnaire are optional (see Section 6.2.3)
[u] The study materials kit will include at a minimum: Individualized PMP, summary of the PMP, Subject Workbook (used for collecting and recording seizure activity information, study drug administration, respiration rate, and other observations made by the caregiver), study drug kit, and dosing instructions.
[v] One study drug kit will be dispensed at Visit 1 and Visit 2. Two study drug kits will be dispensed at Visit 3 and each Visit X.
[w] After Visit 1, telephone follow-up calls with the caregiver(s) and subject (if subject is able to communicate adequately as determined by the investigator) are to occur at least once each month (every 30 days) between visits that are at least 1 month apart until the subject has completed or prematurely discontinued from the study.

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; IRT = Interactive Response Technology system; PMP = Patient Management Plan

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LIST OF ABBREVIATIONS

Abbreviation	Definition or Term
AE	Adverse Event
AED	Antiepileptic drug
ALT	Alanine aminotransferase (same as SGPT)
AP	Alkaline phosphatase
ARS	Acute repetitive seizures
ARTEMIS-1	Acute Rescue Therapy in Epilepsy with Midazolam Intranasal Spray-1
AST	Aspartate aminotransferase (same as SGOT)
AUC_{0-t}	Area under the plasma concentration time curve from time 0 to time of last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration time curve from time 0 extrapolated to infinity
β-HCG	Beta-human chorionic gonadotropin
BP	Blood pressure
BUN	Blood urea nitrogen
B-SIT	Brief Smell Identification Test
CBC	Complete blood count
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CPR	Cardiopulmonary resuscitation
CRO	Clinical research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
EDC	Electronic data capture
EMS	Emergency medical services
ER	Emergency room
ET	Early termination
FDA	Food and Drug Administration
GCP	Guideline for Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Health and Insurance Portability and Accountability Act (of 1996)
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonization
IDs	Identifications
IEC	Independent ethics committee

Abbreviation	Definition or Term
IM	Intramuscular
IN	Intranasal
IND	Investigational new drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITI	Ikano Therapeutics, Inc.
ITIQ	Intranasal Therapy Impact Questionnaire
IUD	Intrauterine device
IV	Intravenous
LAR	Legally acceptable representative
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPEG	Methoxy polyethyleneglycol
NF	The National Formulary
NOAEL	No observable adverse effect level
OAA/S	Observer's Assessment of Alertness/Sedation
PD	Pharmacodynamic
PEG	Polyethylene glycol
PMP	Patient management plan
PK	Pharmacokinetic
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States
USL	Upsher-Smith Laboratories, Inc., (study sponsor)
USL261	Intranasal midazolam, study drug (formerly ITI-111)
USP	United States Pharmacopeia
VNS	Vagus nerve stimulator
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

1.1 Background Information

Seizure clusters, also known as acute repetitive seizures (ARS), occur in a subset of epilepsy patients. Seizure clusters often have distinguishable characteristics that can be recognized by the patients, caregivers, and physician. These characteristics may include a predictable onset, stereotyped auras or other prodrome, or a particular seizure manifestation that is temporally associated with subsequent seizures. Although a patient will usually recover between individual seizures within the cluster, seizure clusters range in duration from several minutes to hours.[1] When a cluster of seizures occurs outside the hospital, patients must often be transported to an acute care facility so that trained medical personnel can administer intravenous (IV) therapy to stop the seizure activity.[2]

Seizure clusters can evolve into prolonged seizures with worsening epileptogenesis if treatment is not prompt and effective.[3, 4] Furthermore, if left untreated, seizure clusters may progress to status epilepticus, a life-threatening, prolonged epileptic crisis.[5] The primary goals of seizure cluster treatment are cessation of the seizure(s) and prevention of seizure recurrence.[1] Acute benzodiazepine treatment is effective for seizure control and often results in rapid termination of the seizure cluster; however, most treatment options rely on intervention by emergency medical personnel and therefore delay treatment while the patient is transported to a medical facility.[6] The development of an easily administered outpatient treatment of seizure clusters may reduce emergency medical intervention and decrease seizure cluster duration. Rectal diazepam gel (Diastat®, Valeant Pharmaceuticals International) is currently available in the United States (US), but has limitations in that a portion of the population does not respond adequately to this treatment.[7] Additionally, the rectal route of administration is more burdensome and may be unacceptable to some patients and caregivers.[7] As such, an approved treatment is needed that effectively terminates seizure cluster activity, has a rapid onset of action, and is easily administered in an outpatient setting.

Midazolam is a benzodiazepine that has inhibitory activity at the GABA-A receptor

resulting in anticonvulsant properties.[8] In adults, midazolam is usually administered IV or intramuscularly (IM) at doses of 1 to 10 mg.[9] In pediatric patients, the dose of midazolam is usually on a mg/kg basis. Like other benzodiazepines, midazolam administration may cause sedation, anxiolysis, and amnesia.[10, 11] Sedative effects usually occur within 5 minutes after IV administration and within 15 minutes after IM administration. Depending on the dose, route of administration, concurrent medications, and patient's age, peak sedation occurs within 30 to 60 minutes after dosing.[12]

Intranasal (IN) midazolam may be safe and effective for the rapid cessation of seizure activity in outpatient settings. Use of intranasal midazolam was originally described in the late 1980s.[10] Over 20 studies in the last 15 years have found midazolam to be a safe and efficacious treatment for seizure control in both adult and pediatric patient populations.[7, 10, 13-31] Furthermore, use of IN midazolam for treatment of seizures has also been advocated by several review articles and editorials.[32-35]

Much of the published work investigating the effects of IN midazolam on seizure control has used midazolam sterile injection solution (5.0 mg/mL) approved for IV delivery administered IN with a needless syringe at doses ≤ 0.6 mg/kg. The delivery of IV-approved midazolam sterile injection solution intranasally has not been optimized, nor is it approved by the US Food and Drug Administration (FDA). In fact, the volume of midazolam sterile injection solution usually ranges from 1 to 2 mL,[11] which exceeds the recommended volume for optimal nasal delivery (≤ 200 µL).[34] Despite the sub-optimal formulation and delivery system, IN delivery of midazolam has been very effective in many settings without major safety concerns. The most common adverse effects have been described as local nasal irritation and discomfort. Unpleasant taste was also commonly reported, suggesting possible oral ingestion of midazolam IV solution, perhaps caused by the suboptimal delivery volumes.[11]

Ikano Therapeutics Inc. (ITI, [previously Intranasal Therapeutics, Inc.]) initiated development of a midazolam rescue treatment designed specifically for IN delivery (ITI-111) for patients who require control of intermittent bouts of seizure activity, including seizure clusters. In June 2010, Upsher-Smith Laboratories, Inc. (USL), obtained exclusive

global rights to ITI-111 (renamed as USL261) assuming all continued development, testing, and clinical trials for the treatment of seizure clusters. The proprietary formulation delivers adequate drug concentrations in a small volume (100 µL). Preliminary human studies show positive pharmacokinetic (PK) and bioavailability properties with good safety and tolerability. The present study was designed to provide extended subject access to USL261 as a treatment option for subjects completing study P261-401 and to establish the long-term safety and tolerability of USL261 (see Section 3, Description of Study).

1.2 Nonclinical Information

To establish the safety, and to supplement the existing body of toxicology data for USL261, four nonclinical studies have been performed using USL261 administered IN (Table 2). These studies included a 14-day IN toxicology study in beagle dogs using the container/closure system (a unit dose spray pump) intended for clinical trials, a 14-day study in rats, a 90-day study in beagle dogs, and a 6-month study in rats. All four studies were conducted in accordance with Good Laboratory Practice (GLP).

Table 2. USL261 Animal Toxicity Studies

Study	Species and Duration	n[a]	Doses mg/day	Sex	Daily Dose (NOAEL)		C_{max} ng/ml [b]	AUC ng*h/L [c]
					mg/day	mg/kg/day		
WIL-637002	Rat – 14 Days	10-15	0, 1, 3, 6	M	6	16.7	1473	330
				F	6	24.5	1747	332
WIL-637001	Dog – 14 Days	4-6	0, 10, 15, 30	M	30	3.3	1226	519
				F	30	4.3	1915	724
WIL-637003	Dog – 90 Days	4-6	0, 20, 30, 60 [d]	M	60	4.9	Daily dose 1: 814 Daily dose 2: 749	914
				F	60	6.5	Daily dose 1: 770 Daily dose 2: 918	803
Experimur 10-610	Rat – 6 Months (3-month interim sacrifice)	20 (10 for the 3-month group)	0, 1, 3, 6 [d]	M	6	19	235	126
				F	6	10	363	270

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; ITI, Ikano Therapeutics Incorporated; NOAEL, no-observable-adverse-effect level.
[a] Number of animals/sex/group varied by treatment.
[b] C_{max} at Day 13 is presented for WIL-637002 and WIL-637001; C_{max} at Day88 is presented for WIL-637003.
[c] AUC_{last} at Day 13 is presented for WIL-637002 and WIL-637001; Total AUC_{0-24} at Day 88 is presented for WIL-637003.
[d] Dosing for WIL-637003 and Experimur 10-610 was twice daily.

USL261 was well tolerated after IN administration to rats (14-day and 6-month dosing) and dogs (14- and 90-day dosing). Acute transient hypoactivity, impaired equilibrium, partial closure of one or both eyes, swaying, and/or transient ataxia (e.g., impaired equilibrium) occurred shortly after dosing in most midazolam-treated groups, and these observations are consistent with the known pharmacological properties of midazolam.

No significant effects on the nasal cavity were observed, and the no-observable-adverse-effect levels (NOAEL) were the maximum doses that could be administered based on midazolam solubility and the maximum volumes that could be ethically administered IN to the animals. The safety of systemic exposure of midazolam has been previously established via a complete set of animal studies as well as clinical experience with midazolam since its

approval in 1985. A complete overview of the preclinical development and pharmacology of midazolam has previously been published.[36]

A 6-month IN study (including a 3-month interim sacrifice group) was conducted in rats (Experimur 10-610). The dose levels and the experimental design were the same as in the 14-day rat study (0, 1, 3, and 6 mg/day). All effects noted were consistent with the 14-day rat study, WIL-637002. Gross necropsy revealed dose-related increases in liver weights, consistent with the known effects of chronic midazolam administration. No other gross lesions or significant findings were noted. Histopathologic examination of the tissues showed no remarkable changes in the nasal tissues or other tissues associated with twice daily nasal administration. Intranasal instillation of Midazolam to Sprague-Dawley rats at dose levels up to 6 mg/day for 6 months was considered well-tolerated. Based on the lack of histological changes observed in this study, the NOAEL (no-observed-adverse-effect level) was considered to be 6 mg/day after 6 months of treatment.

USL261 contains midazolam, EP/ USP in formulation with excipients [redacted]. The effects of the excipient, [redacted], were studied in the 4 completed USL261 nonclinical studies mentioned above. Additionally, a genotoxicology program and a nasal-disposition program in rats and dogs to ascertain the nasal absorption potential of [redacted]0 were completed. Although absorption of the excipient [redacted] via IN administration was detected, all studies completed to date suggest no significant genotoxicity or development/reproductive effects.

In summary, intranasal dosing of high levels of midazolam at high multiples of the clinical doses resulted in no significant changes in any endpoints. Minor clinical signs observed were consistent with the known effects of midazolam by other approved routes of administration.

1.3 Clinical Studies

Table 3 presents a summary of the completed and ongoing studies with USL261. Section 1.3.1 provides additional details on the results of the completed studies.

Table 3. Summary of Completed and Ongoing Clinical Studies with USL261

Protocol No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Administration	Number of Subjects; Age Range	Type of Subjects	Duration of Study	PD and Safety Assessments
Completed Studies							
MZ0714	Evaluate BA, PK, and safety of single doses of USL261; Compare PK and PD of USL261, midazolam IV infusion, and midazolam IV administered IN via needleless syringe.	Open-Label, Five-Way Crossover, Randomized	Subjects received 5 different MZ treatments in random sequence: 2.5, 5.0, or 7.5 mg USL261; 2.5 mg IV MZ infused over 15 min; and 5.0 mg MZ (from IV formulation) administered IN via a needleless syringe	25 Subjects 18 – 45 y	Healthy human volunteers	5 visits in approximately 5-6 weeks, preceded by a screen visit (-1 to -21 days)	SSS, DSST, OAA/S, physical exam, nasal exam, vital signs, TEAEs, oxygen saturation, subject sensory perception
MZ0815	Determine the safety, tolerability, PK and PD of ascending single- and two-dose regimens of USL261	Open-Label	Subjects received IN USL261 at 2 visits. At Visit 1 they received a single dose; at Visit 2 they received 2 doses separated by 15 minutes. A: 2.5 mg/2.5 mg+2.5 mg B:5.0 mg /5.0 mg +2.5 mg C: 5.0 mg /5.0 mg +5.0 mg D. 7.5 mg /7.5 mg +5.0 mg E: 7.5 mg /7.5 mg +7.5 mg	An overall total of 90 subjects (60 adults 18-65 y; 30 adolescents 12-17 y)	Subjects with epilepsy taking stable doses of AEDs	4 visits for a total study duration of approximately 1 ½ to 6 weeks for each subject	SSS, DSST, OAA/S, physical (including nasal) and neurological exams, vital signs, TEAEs, oxygen saturation, subject sensory perception
P261-201	Evaluate the safety, tolerability, PK, and PD of ascending single- and two-dose regimens of USL261 compared with that of placebo	Randomized, Double-Blind, Placebo-Controlled, Dose Escalation	Subjects received a single 10, 15, 17.5, or 20 mg dose of IN USL261 or placebo, followed ≥3 days later by the same total dose or placebo, administered as 2 divided doses 10 minutes apart. Four dose cohorts were completed in ascending order, and dose	60 adult subjects; 18 – 65 y	Subjects with epilepsy taking stable doses of AEDs	4 visits (screening, 2 evaluation visits, and follow-up) over a 7 to 58 day time frame	TEAEs, vital signs, oxygen saturation; SSS, OAA/S, and Coding subtest of Wechsler Adult Intelligence Scale-IV (WAIS-IV)

Protocol No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Administration	Number of Subjects; Age Range	Type of Subjects	Duration of Study	PD and Safety Assessments
			escalation occurred only after review of safety data.				
P261-102	Evaluate the safety, tolerability, PK and PD of USL261 in geriatric and non-geriatric subjects	Randomized, Investigator and subject blind, Sponsor open	Subjects were randomized to receive a single dose of 2.5 and 5.0 mg USL261 at 2 study visits in a crossover fashion.	A total of 30 subjects (12 adult 18-40 y; 18 geriatrics ≥65 y)	Generally healthy geriatric and non-geriatric subjects.	4 visits (screening, 2 evaluation visits, and follow-up) over a 9 to 50 day time frame	TEAEs, vital signs, oxygen saturation; SSS, OAA/S, and DSST
Ongoing Studies							
P261-401	Evaluate the efficacy, safety, and tolerability of USL261 compared with IN placebo for the outpatient treatment of seizure clusters; Evaluate the PK profile of USL261 after administration of 10 mg open-label USL261 (2 single, 5 mg test doses administered 10 min apart)	Randomized, Double-Blind, Placebo-Controlled	Test-Dose Phase: 2 doses of open-label 5.0 mg IN USL261 administered 10 minutes apart. Comparative Phase: subjects are randomized 2:1 to receive 5.0 mg IN USL261 or placebo to be administered during a seizure cluster event, with the possibility of administration of an open-label 5.0 mg IN USL261 dose 10 min to 6 hrs after the double-blind dose.	Planned: a maximum of approximately 240 subjects; ≥12y	Subjects with epilepsy who have seizure clusters	A test-dose phase of up to 28 days, followed by a comparative phase which will be variable, dependent on when the subject experiences a seizure cluster	OAA/S, C-SSRS, physical and neurological exam, vital signs, TEAEs, clinical laboratory evaluations, ECG, pulse oximetry, and need for 2nd dose or emergency treatment

Protocol No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Administration	Number of Subjects; Age Range	Type of Subjects	Duration of Study	PD and Safety Assessments
P261-301	Evaluate the efficacy, safety, and tolerability of USL261 compared with IN placebo for the treatment of intermittent bouts of increased seizure activity in subjects admitted to the EMU	Randomized, Double-Blind, Placebo-Controlled	Eligible subjects will be randomized 1:1 to receive 5.0 mg IN USL261 or placebo.	Planned: approximately 62 subjects; ≥12 y	Subjects with epilepsy admitted to the EMU who present seizure activity that meets defined Treatment Criteria	Screening may occur at EMU admission or up to 28 days prior; Treatment may occur any time during EMU admission with monitoring for up to 6 hrs post-dose; Exit Assessment may occur up to 48 hrs after treatment	TEAEs, clinical laboratory evaluations, vital signs, ECGs (screening only), physical, nasal, and neurological exams, C-SSRS

AED indicates anti-epileptic drugs; BA, bioavailability; C-SSRS, Columbia-Suicide Severity Rating Scale; DSST, Digit Symbol Substitution Test; ECG, electrocardiogram; EMU, epilepsy monitoring unit; IN, intranasal; IV, intravenous; MZ, midazolam; OAA/S, Observer's Assessment of Alertness/Sedation; PD, pharmacodynamic; PK, pharmacokinetic; SSS, Stanford Sleepiness Scale; TEAE, treatment-emergent adverse event.

1.3.1 Results of Completed Studies

1.3.1.1 Study MZ0714

ITI conducted an initial phase I clinical trial (MZ0714) investigating the safety, bioavailability, PK, and pharmacodynamic (PD) properties of USL261 entitled *"A single-dose, open-label, five-way crossover, randomized, bioavailability and pharmacodynamic study comparing intranasal midazolam administration to intravenous midazolam administration in healthy human volunteers."* Safety, bioavailability, PK, and PD parameters for 3 doses of USL261 (2.5 mg, 5.0 mg, and 7.5 mg in 0.1 mL) were compared with administration of IV-approved midazolam sterile injection solution administered IV (2.5 mg in 5 mL) and IN (5.0 mg in 1 mL) via a needleless syringe.

Results suggested that maximum plasma concentration (C_{max}) of midazolam was achieved in all dose groups within 10 minutes to 15 minutes post-administration. The C_{max} for all doses of USL261 were within the range of those achieved following IV and IN administration of midazolam sterile injection solution. USL261 demonstrated linear PK parameters. The absolute bioavailability of all USL261 doses was higher (range: 62% – 73%) than 5.0 mg midazolam sterile injection solution administered intranasally (50%).

Changes in PD measures were dependent on midazolam dose; subjects receiving the highest dose of USL261 (7.5 mg) reported the largest changes from baseline for all PD measures (Stanford Sleepiness Scale, Digit-Symbol Substitution Task, Observers Assessment of Alertness/Sedation [OAA/S]). Route of administration (IV compared with IN) had a significant effect on the PD of midazolam. For example, the maximal sedation effects for all IN midazolam formulations were observed between 45 minutes – 1 hour post-dose; however, maximal sedation occurred within 15 minutes in subjects administered IV midazolam. It is important to note that no significant differences in PD parameters were reported between IN treatments.

Overall, the proportion of subjects who experienced treatment-emergent adverse events (TEAEs) did not increase with ascending doses of IN midazolam. No TEAEs were reported after administration of 2.5 mg IV midazolam. All TEAEs were mild in intensity and the majority of TEAEs (95.7%) were considered related to study drug. No serious adverse events (SAEs) or

deaths were reported, and no subject discontinued due to a TEAE. Overall, the most common drug-related TEAEs (reported by ≥10% of subjects) were increased nasal discomfort (84%), throat irritation (84%), increased lacrimation (76%), dysgeusia (72%), headache (20%), cough (12%), and rhinorrhea (12%). These TEAEs were only observed when midazolam was administered intranasally (IV or IN formulations), which suggested that they were related to route of administration.

1.3.1.2 Study MZ0815

A second phase I clinical trial (MZ0815) also investigated the safety, tolerability, PK, and PD characteristics of USL261 but in adult and adolescent epilepsy patients rather than healthy volunteers. MZ0815 is a multicenter, in-patient study that evaluated an ascending single-dose and 2-dose administration of USL261 (2.5 mg, 5.0 mg, and 7.5 mg) given at 2 study visits separated by ≥ 3 days. USL261 was absorbed rapidly (approximately 13 minutes to 20 minutes after a single dose; approximately 20 to 30 minutes after the 2-dose regimen) and the midazolam C_{max}, area under the plasma concentration time curve from time 0 to time of last measurable concentration (AUC_{0-t}), and area under the plasma concentration time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$) generally increased with total dose. Midazolam C_{max} was lower in adolescents as compared to adults. The mean $t_{1/2}$ ranged from 2.75 to 4.39 hours.

USL261 was deemed safe when administered at doses of 2.5 mg to 15.0 mg (total dose) to adolescent and adult epilepsy patients who were taking concomitant AEDs. Of the 90 enrolled subjects, 88 (98%) experienced at least 1 TEAE. No deaths or SAEs were reported, and no study subject prematurely discontinued due to intolerable AEs. Most TEAEs were mild to moderate in intensity and deemed to be probably related to study drug. The most frequently-reported TEAEs (reported by ≥10% of subjects) associated with study drug were dysgeusia (86%), oropharyngeal pain (57%), rhinalgia (31%), and burning sensation (11%). One subject, who was administered USL261 at a total dose of 12.5 mg, experienced moderate hypoxia approximately 90 minutes after administration of the second dose; however, the event was transient and not associated with sedation, hypoventilation, or changes in vital signs.

1.3.1.3 Study P261-201

Study P261-201 was a single-center, in-patient trial investigating the safety, tolerability, PK, and PD of escalating single- and two-dose regimens of USL261 compared to placebo in adult subjects with epilepsy. Subjects were assigned sequentially to 1 of 4 cohorts to receive either USL261 (10.0 mg, 15.0 mg, 17.5 mg, or 20.0 mg) or placebo at two dosing visits separated by ≥ 3 days. Each subject received USL261 or placebo at Visit 2. At Visit 3, each subject received the same total dose as he/she received at Visit 2 administered as a divided dose.

USL261 was absorbed rapidly (approximately 9 minutes to 19 minutes after a single dose; approximately 19 to 22 minutes after the two-dose regimen). Following either single dose or repeat dose administration, PK parameters for both MZ and 1-OH MZ were similar across cohorts and did not exhibit dose dependent changes. Exposure to MZ and 1-OH MZ (as indicated by C_{max} and AUC parameters) was not dose proportional following single dose or repeat dose administration of 10.0 mg to 20.0 mg. Effects of USL261 on sedation and psychomotor performance were transient following single and repeat dose administration and were consistent across USL261 doses. Consistent with PK results, no dose response was observed in SSS or OAA/S Sum and Composite scores or their corresponding PD parameters from 10.0 to 20.0 mg USL261 following either single or repeat dose administration.

USL261 was generally safe and well-tolerated following single- or repeat-dose administration up to the maximum evaluated total dose level of 20 mg in adult subjects with epilepsy taking concomitant AEDs. In total, 58 subjects (96.7%) reported 179 TEAEs. All of the reported TEAEs were considered mild in severity with the majority (96.0%) were considered "probably related" to study drug. Treatment-emergent AEs reported in ≥20% of subjects in any group were nasal discomfort and throat irritation, which occurred in 96% of subjects administered MDZ NS. However, there was no clear dose relationship and these events also occurred frequently in placebo subjects. Nasal mucosal disorder, headache, dysgeusia, and hiccups were also common TEAEs, occurring in ≥10% MDZ NS subjects.

1.3.1.4 Study P261-102

Study P261-102 was a single-center trial investigating the safety, tolerability, PK, and PD of single 2.5 mg and 5.0 mg doses of USL261 in generally healthy geriatric and non-geriatric subjects. Enrollment was stratified into non-geriatric (18 – 40 years old, inclusive) and geriatric (≥ 65 years old) groups such that there were 12 subjects in the non-geriatric range and 18 subjects in the geriatric range. Subjects were randomly assigned to receive single doses of both 2.5 mg and 5.0 mg USL261 in a 2x2 crossover fashion with a washout period of 4 – 10 days between dosing. Mean systemic exposure (AUC) and peak plasma concentrations (C_{max}) of MDZ were 20–45% higher in the geriatric subjects compared with nongeriatric subjects. Geriatric subjects exhibited greater cognitive effects than nongeriatric subjects, whereas maximum and overall sedation effects were comparable between the two groups.

Of the 30 enrolled subjects, 26 subjects (87%) reported at least one TEAE during the study with more geriatric subjects reporting a TEAE than younger subjects. All reported TEAEs (n=115) were considered mild in severity; most (91.3%) were considered "probably related" to the study drug. No SAEs or deaths were reported, and no subject discontinued study participation due to a TEAE. Although there were some differences between the 2.5 mg and 5.0 mg doses with regard to the incidence of the more frequently reported AEs, there did not appear to be a consistent association with dose.

1.3.1.5 Study P261-401

Study P261-401 is an ongoing, phase III, randomized, double-blind, placebo-controlled, multicenter study of the safety and efficacy of intranasal midazolam in the outpatient treatment of subjects with seizure clusters; the study consists of 2 distinct phases (Test-dose phase and Comparative phase) and 4 study center visits. Subjects need to complete study P261-401 in order to enroll in this study (P261-402).

2 STUDY OBJECTIVES

To evaluate the long-term safety and tolerability of USL-261 in the treatment of seizure clusters

using the following:

- Caregiver-recorded respiration rate at 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours and 4 hours after study drug administration.
- AEs
- Clinical laboratory tests.
- Physical, nasal, and neurological examinations.
- Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiration rate, and temperature) as recorded by the study center personnel.
- B-SIT
- C-SSRS
- Requirement for unscheduled emergency room (ER) or emergency medical service (EMS) visits within 24 hours after study drug administration.

3 DESCRIPTION OF STUDY

3.1 Overview

This is an open-label, multicenter, safety extension study of USL261 in subjects with seizure clusters who have completed study P261-401 (ARTEMIS-1). However if study P261-401 is terminated, subjects who have completed the Test Dose Visit (Visit 2) of study P261-401 will also be eligible to enter this study (P261-402). Each seizure cluster episode will be treated with a single dose of 5.0 mg USL261. A second dose of 5.0 mg USL261 may be given if the seizure cluster has not terminated within 10 minutes after initial study drug administration or if another seizure occurs between 10 minutes and 6 hours after administration of study drug. However, the second dose will not be administered if the subject has a respiratory rate < 8 breaths per minute, requires emergency rescue treatment with assisted breathing or intubation, or has excessive, uncharacteristic sedation (as defined by the investigator in the Patient Management Plan [PMP]). After each USL261-treated seizure cluster episode, the caregiver will call the study center as soon as possible, but no later than 24 hours after USL261administration.

After obtaining informed consent and determining that the subject meets the eligibility requirements for this study, the subject/caregiver will be provided with enough study drug to

treat one seizure cluster episode (1 treatment kit containing two 5.0 mg doses of USL261) at Visit 1. After one USL261-treated seizure cluster, the subject and caregiver will return to the study center for Visit 2 within 120 hours (5 days) of USL261 administration. At Visit 2, the subject/caregiver will again be provided with enough study drug to treat 1 seizure cluster episode (1 treatment kit containing two 5.0 mg doses of USL261). After one USL261-treated seizure cluster, the subject and caregiver will return to the study center for Visit 3 within 120 hours (5 days) of USL261 administration. At Visit 3 and all subsequent visits (except for the Final Visit or Early Termination Visit) the subject/caregiver will be provided with enough study drug to treat 2 seizure cluster episodes (2 treatment kits, each containing two 5.0 mg doses of USL261).

After Visit 3, subjects and caregivers will return to the study center after every second USL261-treated seizure cluster episode. Each of these visits will occur within 120 hours (5 days) after the last USL261 administration.

The duration of each subject's participation will vary and will be up to approximately 4 years from the date of enrollment (Visit 1). After this period, the study duration may be extended until marketing approval or a time period as approved by the Heath Authority where the study is being conducted or sooner, as deemed appropriate by the sponsor, Upsher-Smith Laboratories, Inc. The study will be reviewed on an ongoing basis and immediate discontinuation of the study may occur if: a) safety concerns/issues are noted or have arisen during the conduct of the P261-402 study or other USL261 studies, b) USL261 does not demonstrate efficacy in controlled clinical studies, c) a regulatory authority (regardless of country) requests that clinical studies be interrupted or discontinued, or d) USL discontinues or will discontinue development of USL261. A minimum of 3 days (72 hours) is required between treatments (1 treatment is defined as the use of one or two 5.0 mg doses of USL261 from one study drug treatment kit to treat a single seizure cluster episode). There is no limitation on the total number of seizure cluster episodes treated during the subject's participation in the study.

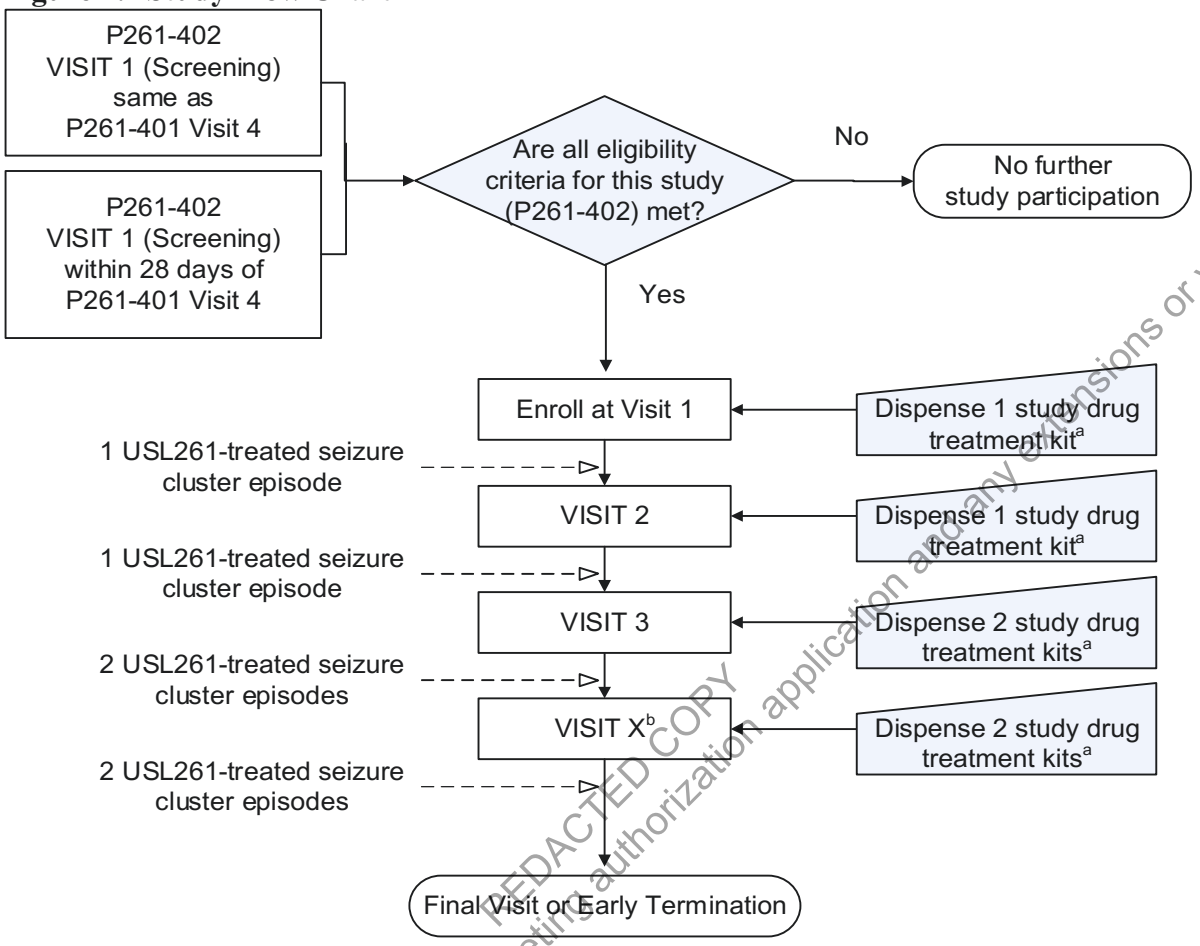
Before any subject is enrolled in this open-label extension study, he/she must have completed study P261-401 or, if Study P261-401 has been terminated, subjects must have completed the Test Dose Visit (Visit 2) of study P261-401. Subjects must meet all other eligibility criteria for

this study. Since enrollment is limited to subjects who have participated in study P261-401, a maximum of 240 subjects (the planned number of subjects completing the Comparative Phase in P261-401) are expected to enroll.

This study will be conducted in accordance with the study protocol, International Conference on Harmonization (ICH) E6, Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements including the US Code of Federal Regulations dealing with clinical studies (21 Code of Federal Regulations [CFR] including § 50, 54, 56 and 312 concerning protection of human subjects, financial disclosure by clinical investigators, Institutional Review Board [IRB] regulations and investigational new drug application, respectively).

A study flow chart is shown in Figure 1, and the Schedule of Procedures is presented in Table 1.

Figure 1. Study Flow Chart



[a] Each study drug treatment kit contains two 5.0 mg doses of USL261
[b] Visits will continue until the Final Visit or Early Termination

3.2 Screening

After subjects and their caregivers have provided informed consent (and, when appropriate, assent), subjects will undergo screening procedures at Visit 1 (which may occur at the same time as or up to 28 days after Visit 4 of the preceding double-blind study P261-401). If Visit 1 of this study (P261-402) is on the same day as Visit 4 of study P261-401, the procedures performed at Visit 4 of study P261-401 that are common to Visit 1 will be used for both studies. If Visit 1 for this study (P261-402) is not on the same day as Visit 4 of P261-401, all necessary procedures will be repeated, except for physical exam, neurological exam, nasal exam, and clinical laboratory testing (hematology, serum chemistry and urinalysis). The time between Visit 4 of

study P261-401 and Visit 1 of study P261-402 will be a maximum of 28 days. The time between Visit 4 of study P261-401 and Visit 1 of study P261-402 may be extended in certain cases; however, the extension must be approved by the Sponsor or CRO designee. If an extension is granted for a given subject, that subject may have to undergo repeat screening laboratory assessments within 28 days prior to dispensing study drug.

If the subject meets the eligibility requirements for this study, the subject/caregiver will be provided with a study materials kit at Visit 1. The study materials kit will contain at a minimum the Subject Workbook, the subject's individualized Patient Management Plan (PMP), summary of PMP, one study drug treatment kit containing two 5.0 mg doses of USL261, and dosing instructions. The PMP will specify at a minimum the criteria for seizure cluster recognition and a rescue protocol individualized for the subject.

3.3 Treatment Phase

Caregivers will administer the first 5.0 mg dose of USL261 at the time of recognition of a seizure cluster that meets study criteria (according to the subject's PMP). A second dose of USL261 5.0 mg may be administered if (a) the treated seizure cluster has not terminated within 10 minutes after the first dose, or (b) another seizure occurs between 10 minutes and 6 hours after administration of the study drug, AND (in both a and b) the subject does not have a respiratory rate < 8 breaths per minute, does not require emergency rescue treatment with assisted breathing or intubation, and does not have excessive, uncharacteristic sedation (as defined by the investigator in the PMP). The caregiver will monitor the subject for 24 hours after study drug administration to record safety and efficacy assessments. The caregiver will call the study center as soon as possible, but no later than 24 hours, after each USL261-treated seizure cluster episode. If seizure cluster activity persists or recurs following the administration of the second dose, caregivers will initiate the rescue protocol as outlined in the subject's PMP.

For Visits 2 and 3, which occur after each of the first 2 USL261-treated seizure cluster episodes, the subject and caregiver will return to the study center within 120 hours (5 days) of study drug administration.

After Visit 3, if the study drug has successfully treated the subject's seizure cluster episodes, the subject has tolerated the study drug treatment well in the judgment of the investigator, and the subject and caregiver have been compliant with the study procedures including completion of the Subject Workbooks and return of the study drug (used and unused), the subject and caregiver will be instructed to return to the study center after every second seizure cluster episode treated with USL261 until the Final Visit or Early Termination. **A minimum of 3 days (72 hours) is required between treatments with study drug**.

All study drug containers dispensed, whether used or unused, and Subject Workbooks are to be returned at the next study visit throughout the study. The study center will make monthly telephone calls between visits to caregiver(s) and subject (if subject is able to communicate adequately as determined by the investigator) when visits are more than 1 month apart. If 6 months pass without the subject having a seizure cluster episode, the subject and caregiver will be asked to come to the study center for re-training on study procedures.

The subject or caregiver will immediately report to the investigator (or his/her designee) as soon as possible any significant medical event (including events that are life-threatening or that result in death, hospitalization or prolonged hospitalization, persistent or significant disability, or incapacity of the subject) that occurs to the subject from the time written informed consent is obtained until completion of the final study visit or 7 days after last administration of study drug , whichever is later. The subject or caregiver may also call the study center at any time during the study for help or advice regarding study procedures.

4 RATIONALE

4.1 Rationale for the Study

This study was designed to provide extended subject access to USL261 as an outpatient treatment option for seizure clusters in subjects with partial or generalized epilepsy with a documented history of seizure clusters who participated in study P261-401 and to establish the long-term safety and tolerability of USL261.

4.2 Rationale for the Study Design

The open-label study design allows subjects who participated in study P261-401 to continue receiving long-term treatment with USL261 at the same investigational dose and to provide long-term safety data of USL261.

4.3 Rationale for the Dosage

The proposed dosage in this study (P261-402) is from the double-blind study (P261-401); therefore, it will be continued in this open-label extension study. The 5.0 mg midazolam USL261 dose is expected to be safe and efficacious, and the 10 mg total dose of USL261 is well within the range of doses correlated with efficacy and has been found to be safe.[18, 31]

The 5.0 mg dose of USL261 used for this phase III trial is based on safety data reported in 2 ITI-sponsored phase I clinical trials as well as the published literature. The ITI-sponsored clinical trials are described briefly below.

- MZ0714: an open-label, 5-way crossover PK/PD safety trial in which 25 healthy adult volunteers were randomly assigned to 1 of 5 treatment sequences. Subjects received single treatments of USL261 at doses of 2.5 mg, 5.0 mg, and 7.5 mg; 2.5 mg midazolam IV infusion over 15-minutes as sterile injection solution; and 5.0 mg midazolam sterile injection solution administered intranasally.
- MZ0815: an open-label, in-patient, PK/PD/safety study of ascending single dose and 2 doses of USL261 (2.5 mg, 5.0 mg, and 7.5 mg) given to 90 adult and adolescent epilepsy patients on separate study visits separated by 3 or more days. At Visit 1, subjects received a single dose of USL261 (2.5 mg, 5.0 mg, or 7.5 mg). At Visit 2, subjects were provided a 2-dose regimen of USL261 with the total dosage ranging from 5.0 mg to 15.0 mg over a 15-minute period. The first dose of USL261 at Visit 2 was identical to the dose strength of USL261 they received at Visit 1. The second dose, administered 15 minutes later, was either identical in strength to previous doses or lower than the previously administered doses.

The PK parameters from the adult subjects in these 2 studies were generally similar, with the exception of AUC values, which were approximately 25% − 39% lower in MZ0815 compared with those in MZ0714. This difference may be due to the different populations studied; healthy adults (MZ0714) versus subjects diagnosed with epilepsy (MZ0815) who were taking concomitant medications, including AEDs known to induce CYP450 3A. Data from MZ0815 showed increasing midazolam plasma concentrations with increasing doses. Midazolam C_{max} was lower in adolescents as compared to adults.

The results from MZ0815 are similar to published PK data for midazolam in adults with epilepsy. In a study of 12 subjects with epilepsy, midazolam was administered IM in doses of 5.0 mg, 7.0 mg, and 10 mg. IM-administered midazolam resulted in a range of mean AUC values from 138 to 167 mg*hr/L and mean C_{max} values from 22 to 78 ng/mL with no report of SAEs, such as respiratory depression.[12] Furthermore, data from the published literature demonstrated that 0.1 to 0.3 mg/kg of the IV formulation of midazolam administered intranasally (5 mg to > 20 mg fixed-dose per subject) effectively terminated seizure activity in most subjects.[21, 25, 39] These doses have seldom caused excessive sedation or respiratory depression.[40]

Based on the current literature, a single 5.0 mg dose of USL261 should provide the majority of subjects the appropriate balance of safety and efficacy. High inter-subject PK variability has been attributed to the cerebral $GABA_A$ receptor binding characteristics of midazolam as well as the drug's complex distribution and metabolism. Therefore, for subjects who do not respond within 10 minutes after administration of 5.0 mg USL261, a second 5.0 mg dose may be administered.

5 SUBJECT SELECTION

5.1 Number of Subjects

Since enrollment is limited to subjects who have participated in Study P261-401, a maximum of 240 subjects (the planned number of subjects completing the Comparative Phase in P261-401) are expected to enroll in the study.

5.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Subject or subject's legally acceptable representative (LAR) has provided written informed consent, and subject has provided written assent where required by local law or Institutional Review Board (IRB)/Independent Ethics Committee (IEC) policy.
2. Subject has a competent, adult (age ≥ 18 years) caregiver(s) who is able to recognize and observe the subject's seizure cluster episodes, who is willing to be trained in the study procedures, and has provided written informed consent; the caregiver(s) must be a relative, partner, friend, or LAR of the subject, or a person who provides daily care to the subject who has a significant personal relationship with the subject.
3. Subject is 12 years of age or older at Visit 1.
4. Subject has an established diagnosis of partial or generalized epilepsy.
5. Subject has a documented history of seizure clusters that includes all of the following:
    a. The subject's seizure cluster pattern is observable, stereotyped, and recognizably different from the subject's other non-cluster seizure activity (if any) in seizure type, duration, severity, or frequency, and of the same type as that approved by the central reviewer in study P261-401.
    b. A documented history of seizure clusters lasting a minimum of 10 minutes from the time the seizure cluster is recognized.
    c. As part of the subject's stereotyped seizure cluster pattern, a second seizure typically occurs within 6 hours from the time of recognition of the seizure cluster.
    d. The subject's stereotyped seizure cluster pattern is composed of multiple (≥ 2) partial or generalized seizures.
    e. The subject's stereotyped seizure cluster pattern was established > 3 months before Visit 1 of study P261-401.
    f. A frequency of ≥ 3 stereotyped seizure clusters during the year before Visit 1 of study P261-401.
    g. At least 1 stereotyped seizure cluster occurring at least once in the 4 months before Visit 1 of study P261-401.

6. Subject has successfully completed study P261-401, and the subject and caregiver have demonstrated adequate compliance with P261-401 study procedures as determined by the investigator OR, if Study P261-401 has been terminated, the subject completed the Test Dose Visit (Visit 2) of Study P261-401 and the subject did not meet any Visit 2 exclusion criteria in Study P261-401.
7. Subject is not likely to conceive, as indicated by a "yes" answer to at least 1 of the following questions:
    a. Is the subject a male?
    b. Is the subject a postmenopausal female as determined in study P261-401?
    c. Is the subject a female who has written medical documentation of being permanently sterilized (e.g. hysterectomy, double oophorectomy, bilateral salpingectomy)?
    d. Has the subject agreed to use two effective methods of contraception during the entire study if she is sexually active or will become sexually active during the study (except where local law or regulation differs; approval by USL or designee is required in such cases)?

       Examples of two effective methods of contraception include the following:
       - A diaphragm and a condom with spermicide
       - An intrauterine device (IUD) used in combination with a barrier method (e.g., condom, diaphragm, or cervical cap with spermicide)
       - Hormonal methods (e.g., high-dose birth control pills, Depo-Provera) or tubal ligation used in combination with a barrier method (e.g., condom, diaphragm, or cervical cap with spermicide)

    Note that hormonal contraception alone is not considered adequate for this study and must be used in combination with another method. The type of birth control used must be approved by the investigator or designee.

5.3 Exclusion Criteria

Any subject who meets 1 or more of the following criteria will be excluded from the study:

1. Subject experienced a seizure cluster progressing to status epilepticus during or since his/her participation in Study P261-401.
2. Subject has a positive pregnancy test at any visit or is pregnant, considering becoming pregnant, or is breastfeeding (female subjects only).
3. Subject who, in the opinion of the investigator, is experiencing an ongoing, uncontrolled, clinically significant adverse event(s) from P261-401 at Visit 1 or did experience a clinically significant adverse event in study P261-401 that might prevent the subject from safely participating in the study.
4. Subject has consumed any clinically significant CYP450 3A inhibitor/inducer, opioid, or other respiratory depressant, not including antiepileptic drugs (AEDs), within the required washout period before Visit 1 (see Appendix 1, Prohibited Concomitant Substances).
5. Subjects using chronic benzodiazepine(s); chronic use is defined as use for 4 or more days in a 7-day period on average.
6. Subject has a neurological disorder that is likely to progress in the next year.
7. Subject has a history of acute narrow-angle glaucoma.
8. Subject has a medical condition including uncontrolled cardiac, pulmonary, renal, hepatic, or gastrointestinal disease that could interfere with the study, subject safety/safety monitoring, or is not stable despite current therapy.
9. Subject has severe chronic cardio-respiratory disease with baseline room air oxygen saturations < 90%, New York Heart Association class III or IV functional status, or the need for ambulatory oxygen.
10. Subject has had psychogenic, non-epileptic seizure(s) during or since the P261-401 study.
11. Subject has suicidality, defined as any of the following: a) active suicidal plan/intent or active suicidal thoughts during or since the P261-401 study as defined by a C-SSRS suicidal ideation score ≥ 3, b) any suicide attempt during or since the P261-401 study as determined by the C-SSRS or medical history, or c) other clinically significant suicidality as determined by the investigator.
12. Subject, in the investigator's opinion, has met the criteria for a major depressive episode during or since the P261-401 study (criteria defined by the current edition of the Diagnostic and Statistical Manual of Mental Disorders).

13. Subject has or has had psychosis during or since the P261-401 study, excluding postictal psychosis.
14. Subject has a history of drug or alcohol abuse during or since study P261-401.
15. Subject has a history of allergy or any significant adverse reaction (including rash) to midazolam.
16. Subject is currently using an investigational drug or device or has used such (other than the study drug during P261-401) within 30 days prior to Visit 1.
17. Subject has plasma phenobarbital concentrations > 35 µg/mL at Visit 1 (phenobarbital concentration will be measured in subjects taking phenobarbital and in subjects for which the investigator deems it necessary).
18. Subject is not appropriate for the study for any other reason as determined by the investigator.

5.4 Informed Consent

Each prospective subject or the subject's LAR will provide written informed consent before any P261-402-specific screening evaluations or other study procedures are performed at Visit 1. Legally acceptable representative is defined as an individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. In addition, each subject's competent caregiver(s) will sign a separate caregiver consent form before any study procedures are performed on the subject.

Informed consent will be given by means of a standard statement, written in non-technical language, which explains the nature of the study, its purpose, procedures, expected duration, alternative therapy available, the benefits and risks involved in study participation, and any discomfort study participation may entail. The investigator or his/her designee must emphasize to the subject, the subject's LAR (if applicable), and the caregiver that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled or affecting subsequent medical treatment or relationship with the treating physician.

The subject, or subject's LAR, will read and consider the statement and be allowed to ask any questions before signing and dating it, and he/she should be given a copy of the signed document. The person conducting the informed consent discussions must personally date and sign the informed consent form (ICF). The investigator will retain the original signed ICF.

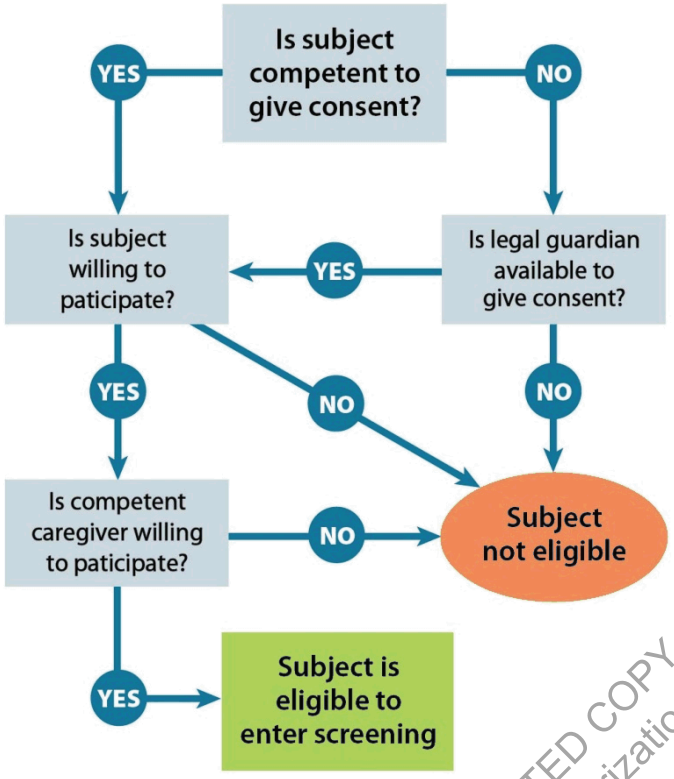
Some subjects will provide written consent in the form of an assent form before any screening evaluation or other study procedure is performed, if required by local law or IRB/IEC policy. In these cases, the ICF will be signed by the subject's LAR. The assent form will provide similar information as the ICF, and the same procedures will be followed as described above for the ICF. The assent form must be signed and dated by the subject and the qualified research professional obtaining the consent.

No subject can enter the study and no study-related procedures can be performed before informed consent has been obtained. The time at which consent was provided will also be recorded on the consent form.

Prior to consenting subjects, the investigator or designee must submit the ICF with the study protocol for IRB/IEC approval. All proposed ICFs must be reviewed and approved by the sponsor or its designee before submission to the IRB/IEC. All informed consent and assent forms will be reviewed by the IRB/IEC and approved (IRB) or a favorable opinion received (IEC) before use in this study. Informed consent will be obtained in a manner consistent with GCP. A copy of the approved version must be provided to the sponsor or the study monitor after IRB approval/IEC favorable opinion.

The flow of informed consent is detailed in Figure 2.

Figure 2. Flow of Informed Consent



5.5 Authorization to Use and Disclose Medical Information

Each subject will be identified by initials (3 letters), date of birth, and a unique study number. In countries where the subjects' initials and/or date of birth cannot be used by local regulations, study centers will use dummy initials and/or year of birth only.

All countries must follow local law(s) for authorization to use and disclose medical information. The remainder of this section (Section 5.5) only applies to study centers in the US.

Under US federal law, subject study records cannot be used or disclosed for research purposes unless an authorization to use and disclose medical information is signed by each subject prior to participation in the study. The investigator or designated assistant will explain to each subject or subject's LAR the purpose of the subject authorization and the disclosures agreed to by signing

the authorization document. Subjects will be given an authorization document and will have the opportunity to ask questions. Subjects must also be informed of the following:

- They may not participate in the study unless the authorization is signed; however, they have the right to revoke this authorization (in writing) at any time.
- If they discontinue from the study, they are not required to revoke the authorization to use and disclose their medical information.
- If they discontinue from the study and do decide to revoke their authorization to use and disclose their medical information, the information that has already been collected in their study records may be used and disclosed as necessary to protect the integrity of the research project.

After this explanation and before any study-specific procedures have been performed, the subject or subject's LAR will voluntarily sign and date an authorization document. Prior to participation in the study, the subject or subject's LAR will receive a copy of the signed and dated written authorization. Authorization to disclose Protected Health Information for research will be obtained in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations 45 CFR Parts 160 and 164.

6 STUDY METHODOLOGY

6.1 Study Procedures

The following section describes in detail all study procedures. A summary table of all required study procedures is presented in Table 1, and the timing for each procedure is described in the appropriate subsection. An electronic case report form (eCRF) is provided for data collection for all subjects.

The duration of each subject's participation will be up to approximately 4 years from the date of enrollment (Visit 1). After this period, the study duration may be extended until marketing approval or a time period as approved by the Heath Authority where the study is being conducted. There is no limitation on the total number of seizure cluster episodes treated during

the subject's participation in the study. Therefore, the number of visits in the study will vary for each subject.

6.1.1 Visit 1 (Screening Visit)

Before any study procedure unique to this study (P261-402) is performed, the subject (or subject's LAR) will provide written informed consent (see Section 5.4, Informed Consent). Procedures at Visit 1 may occur at the same time as Visit 4 of the preceding double-blind study (P261-401) or up to 28 days after Visit 4 of study P261-401. If Visit 1 of this study (P261-402) is on the same day as Visit 4 of study P261-401, the procedures performed at Visit 4 of Study P261-401 that are common to Visit 1 will be used for both studies. If Visit 1 for this study (P261-402) is not on the same day as Visit 4 of P261-401, all necessary procedures will be repeated, except for physical examination, neurological examination, nasal examination, and clinical laboratory testing (hematology, serum chemistry, and urinalysis).

<u>At Visit 1 (Screening)</u>

- Obtain informed consent of subject (or subject's LAR).
- Obtain assent of subject, if applicable.
- Obtain informed consent of caregiver(s).
- Contact Interactive Response Technology (IRT) system to register subject and obtain the study drug kit number.
- Assessment of inclusion/exclusion criteria.
- Caregiver training on study procedures.
- Verify that caregiver has a valid CPR training certificate. If the caregiver does not have one, he/she needs to complete CPR training before the subject/caregiver takes home the study drug.
- Update medical and surgical history from Study P261-401, including seizure history.
- Collect concomitant medications.
- Update PMP, if necessary; PMP must be final before subject receives study materials kit.
- Complete physical, nasal, and neurological examinations.

- Collect blood and urine samples for clinical laboratory testing (serum chemistry, hematology, urinalysis, and phenobarbital levels for subjects taking phenobarbital and subjects for which the investigator deems it necessary).
- Perform urine pregnancy test (all females of childbearing potential; see Section 6.2.2.4).
- Measure height.
- Measure body weight.
- Measure vital signs (BP, HR, respiration rate, temperature).
- Perform C-SSRS, Since Last Visit version.
- Subject and caregiver to complete the outcomes questionnaires (see Section 6.2.3).
- Collect and record AEs.

Eligible subjects/caregivers will receive a study materials kit at Visit 1, which includes the following at minimum:

- Individualized PMP.
- Summary of the PMP.
- Subject Workbook.
- Study drug (1 study drug kit containing two 5.0-mg doses of USL261).
- Dosing instructions.

6.1.2 Visit 2 through Visit X

Visits 2 and 3 will take place within 120 hours (5 days) following each of the first 2 USL261-treated seizure cluster episodes. All subsequent visits will take place within 120 hours (5 days) after every second seizure cluster episode treated with USL261.

At Visits 2, 3, and all subsequent visits (except for the Final Visit or Early Termination Visit), the investigator or other qualified study personnel will perform the following procedures:

- Contact Interactive Response Technology (IRT) system to obtain study drug kit number
- Review, assess, and re-instruct subjects and caregivers on study procedures.
- Verify that caregiver has a valid CPR training certificate. If the caregiver does not have

one, he/she needs to complete CPR training before the subject/caregiver takes home the study drug.

- Collect concomitant therapy.
- Collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since last visit or follow-up phone call.
- Perform physical, nasal, and brief neurological examinations.
- Administer B-SIT (see Section 6.2.2.6)
- Perform clinical laboratory assessments (hematology, serum chemistry, and urinalysis).
- Perform urine pregnancy test (all females of childbearing potential; see Section 6.2.2.4).
- Measure body weight.
- Measure vital signs (BP, HR, respiration rate, temperature).
- Perform C-SSRS, Since Last Visit version.
- Subject and caregiver to complete outcomes questionnaires (see Section 6.2.3).
- Dispense study drug: One study drug kit will be dispensed at Visit 2. Two study drug kits will be dispensed at Visit 3 and all subsequent visits (except for the Final Visit or ET Visit).
- Collect used and unused study drug containers and perform drug accountability.
- Collect and review Subject Workbook and re-dispense new Subject Workbook to caregiver/subject.
- Collect and record AEs.

6.1.3 Treatment – First 2 Years in the Study

During the first 2 years of participation in the study, the caregiver will document in the Subject Workbook all seizure activity that occurs on the day of the seizure cluster (beginning when the seizure cluster is recognized and for 24 hours after the subject receives USL261). Seizure activity will be documented by writing the date and time of onset of each seizure, the date and time of seizure termination, the type of seizure experienced, and any additional treatment intervention (e.g., medication, call for EMS) for each seizure or seizure cluster. Unwitnessed seizures should also be recorded, with the information estimated to the best of the subject's or

caregiver's ability.

When a seizure cluster episode is identified that meets the study criteria as outlined in the subject's individualized PMP, the caregiver will do the following:

- Note the time of recognition of seizure cluster onset (clock time).
- Administer a 5.0 mg dose of USL261 to the subject.
- Note the time that USL261 was administered and the nostril into which it was administered.
- Call the study center as soon as possible, but no later than 24 hours, after study drug administration.
- Measure and record the subject's respiration rate by counting the breaths taken in a 30-second interval at approximately the following times after study drug administration: 10, 15 and 30 minutes, then 1, 2, and 4 hours. Respiration rate will be measured at these times whether or not the seizure cluster has ended, unless, for reasons of subject safety, this assessment cannot be performed.
- Administer the second dose of USL261 5.0 mg if the initial seizure cluster episode has not terminated within 10 minutes after the initial drug administration or another seizure occurs between 10 minutes and 6 hours after administration of the study drug AND the subject does not have a respiratory rate < 8 breaths per minute, does not require emergency rescue treatment with assisted breathing or intubation, and does not have excessive, uncharacteristic sedation (as defined by the investigator in the PMP). If seizure activity persists or recurs following the administration of the second dose, caregivers will initiate the rescue protocol as outlined in the subject's PMP.

When the seizure cluster episode ends, the caregiver will do the following:

- Note and record the time in the Subject Workbook.
- Evaluate the subject's return to baseline functionality by recording the time when the subject was able to return to what he/she was doing in the Subject Workbook.
- Ensure that the Subject Workbook is completed as accurately as possible.

The caregiver will continue to record **all** seizure activity in the Subject Workbook for 24 hours after the subject received study drug. Any changes in the subject's overall health, medications that the subject received, and device use by the subject for 24 hours after the subject received study drug will also be recorded in the Subject Workbook.

Caregivers must contact the study center after every treated cluster episode as soon as possible, but no later than 24 hours after study drug administration.

6.1.4 Treatment – After 2 Years in the Study

After the first 2 years of participation in the study the caregiver will document in the Subject Workbook seizure activity that occurs on the day of the seizure cluster treated with USL261. Seizure activity will be documented by writing the date and time of recognition of the seizure cluster, the date and time of study drug administration (first and second dose, if given), if there is an ongoing seizure at 10 minutes after administration of the first dose (yes/no), start date and time of the first seizure that occurs between 10 minutes and 24 hours from first and second (if given) USL261 dose.

When a seizure cluster episode is identified that meets the study criteria as outlined in the subject's individualized PMP, the caregiver will do the following:

- Note the time of recognition of seizure cluster onset (clock time).
- Administer a 5.0 mg dose of USL261 to the subject.
- Note the time that USL261 was administered and the nostril into which it was administered.
- Call the study site as soon as possible, but no later than 24 hours, after study drug administration.
- Measure and record the subject's respiration rate by counting the breaths taken in a 30-second interval at approximately the following times after study drug administration: 10, 15 and 30 minutes, then 1, 2, and 4 hours. Respiration rate will be measured at these times whether or not the seizure cluster has ended, unless, for reasons of subject safety, this assessment cannot be performed.

- Record if there is ongoing seizure activity at 10 minutes after the first study drug dose (yes/no).
- Record the start time of the next seizure following first study drug dose, if it occurs within 24 hours of the first dose administration.
- Administer the second dose of USL261 5.0 mg if the initial seizure cluster episode has not terminated within 10 minutes after the initial drug administration or another seizure occurs between 10 minutes and 6 hours after administration of the study drug AND the subject does not have a respiratory rate < 8 breaths per minute, does not require emergency rescue treatment with assisted breathing or intubation, and does not have excessive, uncharacteristic sedation (as defined by the investigator in the PMP). If seizure activity persists or recurs following the administration of the second dose, caregivers will initiate the rescue protocol as outlined in the subject's PMP.
- Record the start time of the next seizure following second dose of study drug, if it occurs within 24 hours of the second dose administration.

When the seizure cluster episode ends, the caregiver will do the following:

- Note and record the time in the Subject Workbook.
- Evaluate the subject's return to baseline functionality by recording the time when the subject was able to return to what he/she was doing in the Subject Workbook.
- Ensure that the Subject Workbook is completed as accurately as possible.

The caregiver will record any changes in the subject's overall health, medications that the subject received, and device use by the subject for 24 hours after the subject received study drug in the Subject Workbook.

Caregivers must contact the study center after every treated cluster episode as soon as possible, but no later than 24 hours after study drug administration.

6.1.5 Final Visit or Early Termination Visit

Subjects and caregivers will return to the study center for the Final Visit. Subjects who are

prematurely discontinued or who terminate their study participation after Visit 1 will also have Final Visit / Early Termination (ET) procedures performed as soon as possible, but within 7 days after withdrawal or discontinuation. At the Final Visit or ET Visit, study center staff will collect the following items or information:

- The Subject Workbook (the Subject Workbook will also be reviewed by the study center staff with the caregiver).
- The used and unused study drug container(s) (drug accountability will also be performed).
- Other study materials provided to the subject/caregiver.

Additionally, the following will be measured or performed:

- Contact Interactive Response Technology (IRT) system.
- Concomitant medication review.
- Collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since last visit or follow-up phone call.
- Complete physical, nasal and neurological examinations.
- Administer B-SIT (see Section 6.2.2.6)
- Perform urine pregnancy test (all females of childbearing potential; see Section 6.2.2.4).
- Collect blood and urine samples for clinical laboratory testing (serum chemistry, hematology, urinalysis, and phenobarbital [if necessary]).
- Measure height.
- Measure body weight.
- Measure vital signs (BP, HR, respiration rate, temperature).
- Perform C-SSRS, Since Last Visit version.
- Subject and caregiver to complete outcomes questionnaires (see Section 6.2.3).
- Collect and record AEs.

6.1.6 Telephone Follow-Up and Support

After Visit 1, the study coordinator or designee will call the caregiver(s) and subject (if subject is able to communicate adequately as determined by the investigator) at least once every 30 days (between visits that are at least 1 month apart) until the subject has completed or prematurely discontinued from the study. On these telephone calls, a member of the study center personnel will perform the following at a minimum:

- Verify that at least 1 caregiver is still available.
- Verify that caregiver has a valid CPR training certificate. If the caregiver does not have one, he/she needs to complete CPR training before administering study drug.
- Ask about any seizure clusters that occurred.
- Ask about whether the study drug kit is still accessible and available.
- Review study procedures and retrain, if necessary.
- Answer any questions the caregiver or subject may have about the study or study procedures.
- Collect AEs.
- Collect changes in concomitant medications.
- Collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since last visit or follow-up phone call.

6.1.7 Dosage Instructions

For each seizure cluster episode treated with study drug, subjects will receive USL261 5.0 mg, administered as a single actuation into either nostril. In addition, each subject may receive a second dose of USL261 5.0 mg administered into the opposite nostril if either of the following occurs:

- The seizure cluster has not terminated within 10 minutes after the first 5.0-mg dose of USL261 was administered provided that the subject does not have a respiratory rate < 8 breaths per minute, does not require emergency rescue treatment with assisted breathing or intubation, and does not have excessive, uncharacteristic sedation (as defined by the investigator in the PMP).

OR

- Another seizure occurs between 10 minutes and 6 hours after study drug administration provided that the subject does not have a respiratory rate < 8 breaths per minute, does not require emergency rescue treatment with assisted breathing or intubation, and does not have excessive, uncharacteristic sedation (as defined by the investigator in the PMP).

6.2 Methods of Assessment

6.2.1 Efficacy Assessments

Information recorded in the Subject Workbook (see Section 9.3.2) will be used for analysis of the efficacy endpoints (see Section 10.5.1).

Efficacy will be determined using the following information at a minimum, which will be recorded by the caregiver in the Subject Workbook:

- Date and time of study drug administration.
- Seizure activity:
    - For the first 2 years of participation in the study the date, start, and stop time of each seizure within 24 hours after any study drug administration.
    - After the first 2 years participation in the study the date and start time of next seizure within 10 minutes to 24 hours after administration of the first and second dose of study drug.
- Date and time when subject has returned to full baseline functionality after the treated seizure cluster, as determined by the caregiver. The caregiver will evaluate subject's return to baseline functionality by recording the time when the subject was able to return to what he/she was doing.

6.2.2 Safety Assessments

6.2.2.1 Medical History

Any changes in medical history since the last visit of Study P261-401 will be recorded for each

subject by qualified medical personnel at Visit 1. Changes to medical history during the study will be reviewed by the investigator and noted as an AE, if appropriate.

6.2.2.2 Physical, Nasal, and Neurological Examinations

Physical, nasal, and neurological examinations will be conducted by a qualified investigator or sub-investigator. The complete physical examination will include height and weight measurements, assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, and extremities. The nasal cavity examination will be performed using a nasal speculum.

At Visit 1 (which may occur at the same time as or up to 28 days after Visit 4 of the preceding double-blind Study P261-401), subjects will undergo complete physical, nasal, and neurological examinations. The physical, nasal, and neurological examinations performed at Visit 4 of Study P261-401 will be used for Visit 1 of this study.

At Visits 2, 3, and all subsequent visits (except for the Final Visit or ET Visit), subjects will undergo a complete physical examination, nasal examination, and a brief neurological examination. At the Final Visit or ET Visit, subjects will undergo complete physical, nasal and neurological examinations.

Height will be measured at Visit 1 and the Final Visit or ET Visit only.

Any new clinically significant findings/abnormalities or worsening of Visit 1 findings that meet the definition of an AE must be recorded as both an examination finding and as an AE.

6.2.2.3 Vital Signs

Vital signs will be measured by qualified study personnel at least once during each study visit. At each visit, the following vital signs will be measured while the subject is seated and has been seated for at least 5 minutes:

- Systolic and diastolic BP

- HR
- Respiration rate
- Body temperature

During the study, caregivers will measure respiration rate at approximately 10, 15 and 30 minutes and 1, 2 and 4 hours after study drug administration, and record the findings in the Subject Workbook. To determine respiration rate, the caregiver will count the number of breaths taken by the subject during a 30-second interval and will record the number of breaths in the Subject Workbook. These timed respiration rate measurements will start over if the second dose is given.

6.2.2.4 Clinical Laboratory Assessments

All subjects will have the clinical laboratory tests performed as listed in Table 4. The total volume of blood collected will be approximately 30 mL (2 tablespoons) per subject. Subject fasting is not required before collection of clinical laboratory blood or urine samples.

Female subjects of childbearing potential will undergo urine pregnancy tests for beta-human chorionic gonadotropin (β-hCG) at all visits. Test results must be negative at these visits for a subject to be enrolled or continue in the study. Females of childbearing potential will be those who are not one of the following:

- A postmenopausal female with greater than 1 year since last menses and a FSH value greater than 40 mIU/mL at Visit 1 of study P261-401 or during studies P261-401 and P261-402
- A female who has written documentation of being permanently sterilized (e.g. hysterectomy, double oophorectomy, bilateral salpingectomy). Note that tubal ligation is not considered a permanent form of sterilization for this study.

A report of the laboratory values will be sent to the study center by the central laboratory; the investigator will review the laboratory report and indicate the clinical significance of all abnormal values, and then sign and file the laboratory report in the subject's study file.

Clinically significant laboratory abnormalities will be captured as adverse events. Procedures regarding the acquisition of these specimens and necessary supplies will be provided to all study centers by the central laboratory prior to study initiation.

Table 4. Clinical Laboratory Tests

Hematology (All visits)	**Serum Chemistry (All visits)**
Complete blood count (CBC) with differential	Albumin
Hemoglobin (Hgb)	Alkaline phosphatase (AP)
Hematocrit (Hct)	Alanine aminotransferase (ALT / SGPT)
Mean corpuscular volume (MCV)	Aspartate aminotransferase (AST / SGOT)
Mean corpuscular hemoglobin (MCH)	Bicarbonate
Mean corpuscular hemoglobin concentration (MCHC)	Blood urea nitrogen (BUN)
Platelets	Calcium
Red blood cell (RBC) count	Cholesterol (total)
White blood cell (WBC) count	Chloride
Urine Pregnancy Test (All visits) (Females only)	Creatinine
β-hCG	Gamma-glutamyl transpeptidase (GGT)
Plasma phenobarbital (All visits) [a]	Glucose
	Phosphorus
Urinalysis (All visits)	Potassium
Bilirubin	Sodium
Blood	Total bilirubin
Glucose	Direct bilirubin [b]
Cells (WBC, RBC, epithelial)	Total protein
Ketones	Uric acid
Leukocytes	
Nitrites	
pH	
Protein	
Specific gravity	
Urobilinogen	

[a] For subjects taking phenobarbital and subjects for which the investigator deems it necessary.
[b] Direct bilirubin is done as a reflex if total bilirubin is out of the normal range.

6.2.2.4.1 Sample Collection, Storage, and Shipping

Blood and urinalysis specimens will be collected by qualified study center personnel and sent to and analyzed by a central laboratory for the hematology, urinalysis, serum chemistry, and phenobarbital analyses. Abnormal laboratory test results will be flagged by the central laboratory. Detailed instructions of sample collection, storage, and shipping will be provided by the central laboratory.

Urine pregnancy tests will be performed by qualified research staff at the study center. Blood samples will be collected while the subject is in a seated or supine position.

6.2.2.4.2 Abnormal Clinical Laboratory Findings

Laboratory tests must be repeated if the result is abnormal and clinically significant regardless of causality. The investigator will exercise medical judgment in deciding whether abnormal laboratory values are clinically significant. In some cases, significant changes within the range of normal will require similar judgment by the investigator. If the investigator considers the confirmed abnormal laboratory value to be clinically significant, see Section 7.3 to report as an AE.

6.2.2.5 Columbia-Suicide Severity Rating Scale

The C-SSRS is a clinician-rated scale that assesses suicidal behavior and ideation. The Since Last Visit version will be administered at all visits. The C-SSRS will be administered by qualified, trained raters. In cases where the subject is cognitively impaired and not able to provide responses to the C-SSRS interview, every effort should be made to complete the scale using other sources of information from the subject's medical records, caregiver, LAR, guardian, parent(s), teacher(s), and/or relative(s).

6.2.2.6 Brief Smell Identification Test (B-SIT)

The Brief Smell Identification Test (B-SIT) will be conducted to assess olfactory function. The B-SIT is a brief 12-item, self-administered microencapsulated odorant test for measuring olfactory function.

The B-SIT will be conducted at Visit 2 through X and the Final or ET Visit, except in cases where obtaining this information is not feasible or appropriate, as determined by the investigator. In addition, the B-SIT will be performed only if a validated version in the appropriate language is available.

6.2.3 Outcomes Questionnaires

The outcomes questionnaires should be completed at each visit described below except in cases where the subject or caregiver refuses or obtaining this information is not feasible; in these situations the questionnaires listed below are optional.

6.2.3.1 SF-12v2 Health Survey (SF-12v2)

The SF-12v2 is a 7-question, short-form health survey that is designed to collect data on patient and caregiver health-related quality of life. The SF-12v2 will be self-administered by both the subject and by the caregiver individually at Visit 1 and the Final Visit or ET Visit.

6.2.3.2 Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM is a general measure of a patient's overall satisfaction with his/her medication. The TSQM will be self-administered by the subject at all visits.

6.2.3.3 Intranasal Therapy Impact Questionnaire (ITIQ)

The ITIQ is a questionnaire that collects data regarding a patient's or a caregiver's perception of how having access to an intranasal seizure therapy might impact their lives. It contains 2 questions. The ITIQ will be self-administered by both the subject and the caregiver individually at all visits.

6.2.3.4 Caregiver Questionnaire

The Caregiver Questionnaire is self-administered by the primary caregiver and consists of Caregiver demographics (completed at Visit 1 or if there is a change in primary caregiver during the study).

6.2.4 Treatment Compliance

Outpatient treatment compliance will be determined by the return of used and unused study medication, as well as the dosing information recorded in the Subject Workbook.

6.3 Prior and Concomitant Therapy

Any changes in medication / device use since the last visit of Study P261-401 will be recorded for each subject by qualified medical personnel at Visit 1.

If the subject is using or has used any of the food, beverage, or medicinal products listed in Appendix 1, Prohibited Concomitant Substances since completion of study P261-401, the investigator or designee will inform the subject of the required washout period.

Concomitant therapy is defined as any medication (prescription or non-prescription), nutritional supplement, herbal preparation or device use (e.g., VNS magnet) taken or used from Visit 1 through the Final Visit or ET Visit. Concomitant therapy will be updated with any changes at each study visit.

6.3.1 Permitted Medications and Devices

A subject's AED regimen (with or without intermittent use of benzodiazepines) may be adjusted during this open-label study, but changes must be recorded in the Subject Workbook. Similarly, vagus nerve stimulator (VNS) settings may be adjusted, but changes must be recorded in the Subject Workbook. The use of a magnet with the VNS must also be documented in the Subject Workbook.

Use of sedating antihistamines and alcohol is allowed during the study. However, the subject and caregiver should be instructed that sedating antihistamines and alcohol are not to be used for at least 24 hours after study drug administration. In addition, caregivers should be instructed to forego administration of the study drug within the 24 hours after a subject takes a sedating antihistamine or uses alcohol.

6.3.2 Prohibited Substances

None of the medications listed in Appendix 1, Prohibited Concomitant Substances, are permitted during the study period. This includes CYP450 3A inhibitors /inducers, opioids, other respiratory depressants and other sedating medications. If a subject is or was taking any of these medications at or before the Screening Visit, the subject must discontinue the prohibited substance and return for Visit 1 after at least the minimum washout time shown in Appendix 1. However, Visit 1 may not occur more 28 days after Visit 4 of Study P261-401. The time between Visit 4 of study P261-401 and Visit 1 of study P261-402 may be extended in certain cases; however, the extension must be approved by the Sponsor or CRO designee. If an extension is granted for a given subject, that subject may have to undergo repeat screening laboratory assessments within 28 days before Visit 2.

If a subject takes any of these medications after Visit 1 and the usage is chronic or to be taken on recurring basis, the subject should be discontinued from study. If the usage of that medication is/was temporary and not expected to be recurrent, the subject should not take the study medication until the time between the last dose of that substance and the date allowable to resume study medication for a qualifying seizure cluster is equal to or greater than the minimum washout shown in Appendix 1, Prohibited Concomitant Substances. The subject and/or caregiver should be reinstructed on prohibited medications.

6.3.3 Use of Benzodiazepines

Benzodiazepines that are used for rescue therapy of seizures or for non-epilepsy indications are allowed provided they are typically used ≤ 3 days in a 7-day period on average. Benzodiazepines for rescue therapy of seizures or for non-epilepsy indications are not to be used within 24 hours prior to study drug administration and not for at least 6 hours after study drug administration.

Use of a benzodiazepine as a chronic AED (more than 3 days per week on average) is not permitted.

6.4 Restrictions during the Study

6.4.1 Activity Restrictions

There are no restrictions on subject activity required by this study.

6.4.2 Food and Fluid Intake

Foods and beverages that are not permitted during the study (from Visits 1 through the Final Visit or ET Visit) include star fruit (see Appendix 1, Prohibited Concomitant Substances, for a complete list). Consuming these substances during the study may alter the subjects' response to treatment with midazolam. For this reason subjects consuming these substances during the study may be withdrawn (terminated) from the study.

If a subject consumes any of these substances, the subject should not take the study medication until the time between the last dose of that substance and the date allowable to resume study medication for a qualifying seizure cluster is equal to or greater than the minimum washout shown in Appendix 1, Prohibited Concomitant Substances. The subject and/or caregiver should be reinstructed on prohibited food and beverage substances.

6.5 Subject Withdrawal or Discontinuation

A subject may voluntarily withdraw from participation in the study at any time for any reason. Similarly, a subject's caregiver may withdraw from study participation at any time. If the caregiver withdraws from the study without a suitable, trained replacement, the subject will be discontinued from the study. The investigator or sponsor may also withdraw the subject from further participation in the study at any time, if it is considered in the best interest of the subject or the study, without prejudice to the subject's future medical care. The investigator may also discontinue a subject's study participation if the subject has not experienced a seizure cluster meeting the study criteria within 6 months after enrollment in the open-label study. A subject who prematurely discontinues from the study should return to the study center within 7 days to undergo the ET visit evaluations.

The primary reason for a subject's premature discontinuation from the study should be selected from the following standard categories and documented in the source documents:

- **Adverse event:** One or more clinical or laboratory events which, in the medical judgment of the investigator, are grounds for discontinuation even if the event does not appear to be related to study medication. The subject may withdraw because of an AE even if the investigator does not feel that it is grounds for discontinuation. This category includes subject death.
- **Withdrawal of consent:** Subject or Caregiver desires to withdraw from further participation in the study.
- **Lost to follow-up:** In the case of subjects who do not return for study visits and cannot be contacted, vigorous and repeated attempts (minimum of 3) by study center personnel to contact the subject should be made and recorded in the source data, e.g., telephone reports, letters, progress notes. Attempts to contact the subject must include at least 1 certified mail receipt. If all attempts to contact the subject have failed that subject is considered to be lost to follow-up and discontinued from the study.
- **Protocol violation:** Failure to adhere to the protocol requirements (e.g., subject's caregiver withdraws from the study without a suitable replacement).
- **Subject has not experienced a seizure cluster meeting the study criteria within 6 months after enrollment.**
- **Pregnancy:** Subject pregnancy.
- **Administrative/Other:** Premature termination for reason other than the above, such as illness of investigator, theft or loss of study drug, or termination of study by study sponsor.

6.5.1 Withdrawal or Discontinuation Procedures

If a subject withdraws or is discontinued prematurely from the study, the investigator must document the primary reason for discontinuation in the source documents and appropriate eCRF, and the investigator should make every effort to perform all ET Visit evaluations. In the event that a subject elects not to return to the study center for the ET Visit, the investigator must make

every effort to contact the subject to review all AEs. If a subject discontinues prematurely due to an AE or SAE, the event will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator to be no longer clinically significant. In the case of subjects who do not return for study visits and cannot be contacted, vigorous and repeated attempts (minimum of 3) by the study center personnel to contact the subject should be made and recorded in the source data, e.g., telephone reports, letters, progress notes. Attempts to contact the subject must include at least 1 certified mail receipt.

Subjects who prematurely discontinue from the study will not be replaced.

6.6 Treating Overdose

Refer to the Midazolam Injection, USP, Package Insert (Hospira) for full details on midazolam overdose (see Appendix 2). In the case of suspected overdose, respiration, HR, and BP should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation, including administration of oxygen. An IV infusion should be started. Should hypotension develop, treatment may include IV fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis, or hemodialysis is of any value in the treatment of midazolam overdose. 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. However, the reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients. The prescriber should be aware of a risk of seizure in association with flumazenil treatment.

An overdose is not recorded as an AE unless signs or symptoms of the overdose occur, in which case the signs or symptoms are recorded as AEs and attributed to the overdose of study drug.

6.7 Pregnancy

If any female subject becomes pregnant while enrolled in the study, she must be discontinued from the study and undergo the ET Visit evaluations. The investigator or designee must notify USL or its designee within 24 hours of learning about the pregnancy. The investigator or designee must complete the Pregnancy Notification Form provided by USL or its designee. The investigator or designee must diligently follow the subject until delivery or termination of the pregnancy, providing necessary updated information to USL or its designee. Information on the status of the mother and the child will also be forwarded to USL or its designee. Generally, follow-up will occur within 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will also be reported.

Although pregnancy occurring in a clinical study is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and will be followed as such. A spontaneous abortion is always considered to be a SAE.

7 ADVERSE EVENT MANAGEMENT

7.1 Definitions: Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product whether or not a causal relationship with this treatment exists.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples of AEs include, but are not limited to, the following:

- Exacerbation of a pre-existing illness following the start of the study.
- Increase in frequency or intensity of a pre-existing episodic event or condition.

- Condition detected or diagnosed after the start of the study even though it may have been present prior to the start of the study.
- Condition that leads to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion) may be an AE, but the procedure itself is not an AE.

An AE does not include the following:

- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not represent a worsening of the disease or condition.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery; medical or surgical procedures such as endoscopy, tooth extraction, or transfusion; social and/or convenience admissions).
- The disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe or at an increased frequency than that expected for the subject's condition. Accordingly, seizures in this subject population are anticipated, and therefore will not be considered AEs unless the investigator deems a particular seizure(s) to represent a worsening of the patient's seizure disorder. Seizures that result in hospitalization or are considered to be medically significant will be considered to be SAEs and will be reported as stated in Section 7.2.
- Overdose of either study drug or concurrent medication without any signs or symptoms.

The investigator will evaluate AEs using the following guidelines:

- **Description of Event** (if the event consists of a cluster of signs and symptoms, a diagnosis should be recorded [e.g., flu syndrome] rather than each sign and symptom).
- **Onset Date**
- **Stop Date**
- **Intensity** should be recorded as mild, moderate, or severe. Intensity is defined as one of the following:
    - **Mild***:* awareness of sign or symptom, but easily tolerated
    - **Moderate**: discomfort sufficient to cause interference with normal activities

- **Severe**: incapacitating, with inability to perform normal activities

It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity; whereas seriousness is defined by the criteria provided below. An AE of severe intensity need not necessarily be considered serious. For example, a migraine headache that incapacitates a subject for many hours may be considered a severe AE but not a SAE.

- **Seriousness**: As provided in FDA Title 21 CFR Part 312.32 (a) and the guidelines of ICH GCP (CPMP/ICH/135/95), an SAE is any untoward medical occurrence that at any dose:

  - **Results in death**
  - **Is life-threatening**: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have become life-threatening or caused death if it were more severe.
  - **Requires inpatient hospitalization or prolongation of existing hospitalization**: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE. Hospitalization requires an admission to the hospital.
  - **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.**
  - **Is a congenital anomaly/birth defect**: See Pregnancy Information (Section 6.7 Pregnancy).
  - **Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above should also be considered serious**. Examples of such events are intensive treatment in an ER or at home for allergic bronchospasm, or

blood dyscrasias that do not result in hospitalization; or development of drug dependency or drug abuse.

For this study, the diagnosis of status epilepticus (as determined by the investigator) will ALWAYS be considered serious and follow the procedure for reporting SAEs.

The investigator must record whether or not the AE meets the definition of serious. If the event is serious, the investigator must complete an SAE Report Form.

- **Relationship** to Study Drug

The investigator must make a causality assessment (relationship to study drug) based on the following four causality terms:

  - **Related**: Study drug and AE occurrence definitely related in time and AE more clearly or more likely explained by study drug exposure than by other mechanism.
  - **Possibly Related**: Study drug administration and AE occurrence reasonably related in time and the AE explained equally well by causes other than study drug.
  - **Unlikely Related**: Study drug administration and AE occurrence is not reasonably correlated with study drug administration or the AE is possibly explained by another cause.
  - **Not Related**: The time or occurrence of the AE is not correlated with study drug administration or the AE is clearly explained by another cause.

- **Frequency**: The investigator must record whether the AE is a single event or an intermittent event (an AE that occurs more than once and each event is considered to be of the same intensity/not worsening).
- **Outcome**: Outcome of AEs should be recorded as resolved, resolved with sequelae, not resolved, improved, or fatal. If an AE is not resolved at the time of discontinuation, the AE should be followed until it is resolved (returns to normal or baseline) or the subject's condition has stabilized, or until it is judged by the investigator to be no longer clinically significant or, when applicable, the subject is receiving appropriate medical care.
- **Action Taken**: All applicable action(s) taken with regard to study drug should be recorded as either no change, permanent discontinuation or temporarily stopped

7.2 Reporting of Adverse Events and Serious Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in Section 7.1. All AEs and SAEs that are observed, queried, or spontaneously volunteered by the subjects occurring from the time written informed consent is obtained until completion of the final study visit (Final Visit or ET visit) or 7 days after last administration of study drug, whichever is later, will be recorded in the source documents and will be entered on the appropriate eCRF even if the AE is assessed by the investigator as not related to study drug. Information to be collected includes the nature, date of onset, stop date, intensity, duration, treatment, causality, and outcome of the event. SAEs that occur after completion of the final study visit (Final Visit or ET visit) or 7 days following the last administration of study drug, whichever is later, will be collected only if they are considered by the investigator to be related to study drug.

All SAEs, regardless of expectedness or causality, must be reported on the SAE Report Form by email or fax to designated Clinical Research Organization (CRO) [inVentiv Health Clinical] immediately, but no later than 1 business day of the Investigator's or any other study center personnel's knowledge of the event. In the event of any fatal or life-threatening SAE, the investigator must also inform a Medical Monitor at inVentiv Health Clinical by telephone or email immediately. In addition, any AE resulting in permanent study discontinuation for a subject must be reported within 2 business days to inVentiv Health Clinical.

A completed SAE Report Form and pertinent source documents (e.g., relevant medical records or pages from Subject Workbook) should be emailed or faxed to inVentiv Health Clinical within 1 business day of the investigator's or any study center personnel's knowledge of a SAE. An updated SAE Report Form should be emailed or faxed to inVentiv Health Clinical within 1 business day of receipt of new / updated information. The SAE Reporting Requirements are outlined in Table 5.

Table 5. Serious Adverse Event Reporting Requirements

Type of AE	Reporting Time Frame	Reporting Method	Telephone Number, Fax Number, or e-mail address
All SAEs, including fatal or life-threatening SAEs	Immediate but no later than 1 business day	E-mail or Fax the SAE report form[a]	**United States and Canada:** E-mail: SAEReportingUS@pharmanet-i3.com Fax #: +1-609-951-6670 **Rest of World:** E-mail: SAEReportingUS@pharmanet-i3.com Fax #: +44-1628-461141
Fatal or Life-Threatening SAEs	Immediate	Telephone or E-mail Medical Monitor[b]	**North and South America:** [redacted] (mobile) [redacted] (e-mail) **Rest of World:** [redacted] (office) (mobile) [redacted] (e-mail)
	Immediate but no later than 1 business day	E-mail or Fax the SAE report form[a]	**United States and Canada:** Email: SAEReportingUS@pharmanet-i3.com Fax #: 1-609-951-6670 **Rest of World:** Email: SAEReportingUS@pharmanet-i3.com Fax #: +44-1628-461141

[a] E-mail is the preferred method for SAE report forms
[b] Telephone is the preferred method for immediate contact after a fatal or life-threatening SAE

The investigator will comply with the applicable local regulatory requirements related to reporting of SAEs to their IRB / IEC.

All AEs and SAEs must be followed until they are resolved (return to normal or baseline) or the subject's condition has stabilized, or until they are judged by the investigator to be no longer

clinically significant. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. If the subject dies, a death certificate and any available postmortem findings (including histopathology) must be provided to USL (or its designee).

7.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal laboratory findings should not be listed on the AE eCRF page unless signs or symptoms are present or the laboratory finding is deemed clinically significant by the investigator (confirmed by repeat laboratory testing). If a laboratory value or assessment is related to a medically defined new or worsening of a pre-existing diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE eCRF page, not the individual laboratory values. If a medically defined diagnosis or syndrome cannot be made and the subject is asymptomatic, a clinically significant laboratory value will be recorded as an AE.

All clinically significant abnormal laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or stabilize, or until they are judged by the Investigator to be no longer clinically significant.

8 RANDOMIZATION AND BLINDING METHODS

8.1 Randomization

Randomization is not needed for this study as all subjects will receive open-label USL261. Each subject will retain the study identification number from the P261-401 study for use in this study.

8.2 Blinding

Study drug will not be blinded as this is an open-label study.

9 MATERIALS AND SUPPLIES

9.1 Study Drug

USL261 contains midazolam, EP/USP as the active ingredient, and the inactive ingredients [redacted] A 5.0 mg dose of USL261 (0.1 mL dose of a filtered midazolam 50 mg/mL solution) is delivered with a single actuation of the unit dose pump. The dosage unit contains sufficient solution to provide a single 5.0 mg dose of USL261 and overfill for the pump to work correctly.

USL261 is designated as a Schedule IV controlled substance with abuse potential by the US Controlled Substances Act (21 Code of Federal Regulations [CFR] §1308).

9.1.1 Controlled Substance Documentation

Midazolam is a controlled substance (Schedule IV) under the US Controlled Substances Act (21 CFR §1308). Prior to shipment of study drug, the investigator must provide USL or designee with a copy of a controlled substance license (or local country equivalent) that clearly identifies the registrant and address of the registrant. Study drug supplies will be shipped to the registrant and address noted on the certificate.

9.2 Study Drug Labeling

USL261 nasal spray containers will be provided as ready-to-use assemblies packaged to prevent accidental actuation. The drug product utilizes a Unit Dose Nasal Spray System consisting of a stoppered glass vial containing study drug which is inserted into a vial holder, which is in turn held in a white plastic nasal spray actuator. The vial holder is pushed into the nasal actuator, which sprays the dose out of the nasal spray actuator tip.

Study drug will be shipped to an authorized and licensed drug distribution company or companies for labeling and packaging. Since the active drug product is classified as a Schedule IV Controlled Substance (21 CFR §1308), all clinical supplies will be stored,

distributed, and destroyed in compliance with US Drug Enforcement Administration (DEA) regulations (or local country equivalent).

The study drug supplies will be labeled appropriate to their use. USL261 5.0 mg containers will be identified as open-label treatments. The label will contain at a minimum the following information for the US (additional items will be added as required for other study countries):

- Protocol number
- Name of drug
- Kit identification number
- Instructions for use

"Caution: New Drug – Limited by Federal law to investigational use" will also appear on the immediate package of each nasal spray product used during the study as required by 21 CFR §312.6.

9.3 Additional Study Supplies

9.3.1 Patient Management Plan

The individualized PMP prepared for each subject during the double-blind study P261-401 will be used for this study (P261-402). The PMP contains the following information at a minimum:

- A description of the seizure cluster eligible for treatment with study drug.
- A definition of what is to be considered excessive, uncharacteristic sedation for the patient.
- Instructions for the caregiver on when to administer study drug.
- A Rescue Protocol for persistent or recurrent seizure activity or other safety concern.

The PMP will be updated with any necessary changes during Visit 1. Any changes to the PMP must be finalized before the subject / caregiver receives the study materials kit to take home.

The description of the subject's seizure cluster pattern must be the same as that approved by the central reviewer in study P261-401. Only editorial updates are allowed to the seizure cluster

description in the PMP. Updates to the Rescue Protocol and other sections of the PMP are allowed.

Subjects and caregivers will receive a copy of the PMP at Visit 1. A summary of the PMP (i.e., laminated card for convenient reference) will also be provided.

9.3.2 Subject Workbook

Subjects and caregivers will receive a Subject Workbook at each visit except the Final or ET Visit. In this study, the Subject Workbook is a critical source document for collecting and recording outpatient information during the Treatment phase of this study. The Subject Workbook will be used to record the following:

- Seizure activity:
    - For the first 2 years of participation in the study seizure activity that occurs in the 24 hours after study drug is administered will be documented by legibly recording the date and time of onset of each seizure, the date and time of seizure termination, the type of seizure experienced, and any treatment intervention (e.g., medication, call for EMS), for each seizure or seizure cluster. Unwitnessed seizures should also be recorded, with the information (e.g., date, seizure start, and stop time) estimated to the best of the caregiver's ability.
    - After the first 2 years participation in the study seizure activity will be documented by legibly recording the date and time of recognition of the seizure cluster, if there is ongoing seizure activity at 10 minutes after administration of the first dose (yes/no), start date and time of the first seizure that occurs between 10 minutes and 24 hours from first and second (if given) USL261 dose.
- The date and time of study drug administration.
- The subject's respiration rate at specified time points after study drug administration.
- The date and time of return to baseline function after the treated seizure cluster (as assessed by the caregiver).

- Medications that the subject received and device use by the subject within 24 hours after study drug administration
- Changes in the subject's overall health in the 24 hours after study drug administration.
- Changes in medication type and/or dosing.
- All other safety observations.

The Subject Workbook will also contain information and instructions for administering study drug, assessing respiration rate, and completing the Subject Workbook. The caregiver will be instructed by the study center personnel as to how to complete the Subject Workbook. The subject or caregiver is required to return the completed Subject Workbook to qualified research staff at each follow-up visit (Visits 2 through the Final Visit or ET Visit). A new Subject Workbook will be dispensed at each subsequent visit (except the Final or ET Visit).

9.3.3 Caregiver Training

Caregivers will be trained in study procedures by qualified study personnel at Visit 1 and retrained as needed at each follow-up visit and/or telephone follow-up call. If 6 months pass without the subject having a seizure cluster episode, the subject and caregiver will be asked to come to the study center for re-training on study procedures. Topics of the caregiver training will include, but are not limited to the following:

- Overview of the study.
- Training on the subject's individualized PMP, including how to recognize the subject's seizure cluster episode and when contact EMS or go to the ER.
- How and when to give the study drug.
- Performing study assessments (e.g., measuring respiration rate, seizure diary, etc.)
- Completing the Subject Workbook.

Caregivers are also required to have a current CPR training certificate throughout the entire study.

9.4 Study Drug Inventory and Storage

USL requires sponsored investigators to maintain adequate drug inventory and security at all times. Upon receipt of the study drug, the investigator or designee will perform an inventory of the shipment, comparing the shipment inventory to actual study drug received, and complete and sign an inventory log. The investigator or designee must count and verify that the shipment contains all the items appearing on the shipment inventory. The investigator must immediately notify USL (or designee) or the drug distribution contractor of any damaged or unusable study drug that the study center receives, and document any damaged or unusable study drug in the inventory log.

Only after receipt of all required documentation from a clinical study center will USL or its designee notify the drug distribution contractor to distribute the initial study drug to that center. Additional study drug will be shipped as needed. The investigator or designee will retain a copy of the shipment inventory received with the drug supply in the study file. Each time study drug is dispensed to a subject / caregiver, the investigator or designee will record the quantity and a description (e.g., kit identification code, subject identification number) on the drug accountability log. The investigator / designee will also document any subsequent returns or losses of study drug on the drug accountability log.

Drug accountability records will be available to the study monitor for review at each site visit. The study monitor will inspect drug supplies and accountability records throughout the study conduct at the study center to confirm inventory control and proper study drug storage. The study monitor will record any discrepancies and/or deficiencies and report them to the investigator and to USL or designee and will document the investigator's plan for resolution of any drug inventory or storage issues.

9.4.1 Drug Storage at Research Centers

Since midazolam is a controlled substance (Schedule IV), drug supplies must be kept in a secure, double-locked, substantially constructed enclosure to which access is limited (e.g., locked cabinet inside a locked room). The investigator will take adequate precautions, including locked

storage, to prevent theft or diversion of the study drug, consistent with 21 CFR § 312.69. Within the locked storage area, study drug will be stored in accordance with the conditions specified on the drug labels until dispensed (i.e., controlled room temperature, with excursions between 15° and 30°C [59° and 86°F]).

Before an investigator is allowed to participate in this study, the drug storage area at his/her study center must be inspected by USL or designee. The study monitor (or designee) will also discuss drug storage responsibilities with the investigator.

9.4.2 Dispensing of Study Drug

All study drug will be dispensed by the study center pharmacist or other qualified individual, and each study drug kit dispensed will be documented in the drug accountability log. Study drug will be dispensed as follows:

- Visits 1 and 2: dispense 1 study drug kit at each visit.
- Visits 3 and each subsequent visit (except for the Final Visit or ET Visit): dispense 2 study drug kits at each visit.

Each study drug kit will consist of two 5.0 mg doses of USL261. When dispensing the study drug, qualified study center personnel will also tell or remind subjects/caregivers: (1) to store study drug at room temperature (see Section 9.4.1, Drug Storage at Research Centers); and (2) to return study drug containers (used or unused) to study center staff at the next visit.

9.4.3 Return or Destruction of Study Drug

At Visits 2, 3 and every visit thereafter, the subject / caregiver must return all used and unused study drug containers to the study center, which the staff will collect for reconciliation.

At the conclusion of the study, the Study Monitor (or designee) and investigator (or designee) will perform a final inventory of study drug shipped to, dispensed by, and remaining at the site. This reconciliation will be logged on the drug accountability form, which will then be signed and dated. If any supplies are missing, this discrepancy must be indicated on the drug

accountability / return forms together with an explanation of the discrepancy. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. The investigator or designee must return all used and unused medication to USL or designee unless alternative arrangements for drug disposal are authorized by USL. Drug accountability records should be returned to USL, and the investigator or designee must retain copies of these drug accountability records for his/her files in accordance with 21 CFR § 312.59.

No study drug will be retained at any clinical site when the study is completed; all study drug will be returned to USL or its designee.

10 DATA ANALYSIS AND STATISTICAL PROCEDURES

All statistical analyses will be performed using appropriate procedures in SAS version 9.2 or higher. No hypothesis tests will be conducted.

Data will be listed and tabulated overall. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Categorical data will be presented using counts and percentages.

Detailed descriptions of all definitions and analyses will be available in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock.

10.1 Populations for Analysis

Safety Population: The Safety Population includes all subjects who are enrolled in the open-label study and received at least one dose of open-label study drug.

Efficacy Evaluable Population: The Efficacy Evaluable Population includes all subjects in the Safety Population who received at least 1 dose of study drug during the open-label study and who have any post-treatment efficacy assessment.

10.2 Subject Disposition

A summary of subject disposition will display the number of subjects who completed study P261 401, were screened for the open-label study P261-402, enrolled in the open-label study P261-402, and received open-label study drug. The number of subjects who discontinued will be summarized according to the primary reason for withdrawal.

The number of seizure cluster episodes treated with USL261 will also be summarized.

Descriptive statistics of the demographic profile and baseline characteristics will be summarized for the Safety Population. No formal statistical analyses of these data are planned.

10.3 Medical and Surgical History

Updates to medical and surgical history from the end of study P261-401 and during this study will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA®) and will be listed.

10.4 Prior and Concomitant Therapy

All medications will be classified according to the World Health Organization (WHO) Drug Dictionary and the incidences will be tabulated by drug class and/or generic name for the Safety Population. Concomitant drug therapy will include all medications (prescription or non-prescription), nutritional supplement, herbal preparation or devices (e.g., VNS) taken/used from the date of enrollment in the open-label study through the Final Visit or ET Visit. Concomitant AEDs will be summarized separately.

10.5 Safety and Efficacy Endpoints

The data to assess the safety and efficacy endpoints will be obtained from the Subject Workbooks, which include a seizure diary, and safety data collected at each visit as entered into the Electronic Data Capture (EDC) system.

10.5.1 Safety Analyses

Evaluation of safety will be performed for all subjects in the safety population. Besides regular summary tabulations, additional safety analyses may be conducted to account for the potential difference in drug exposure or follow-up time among patients. Further details on the analysis will be provided in the SAP prior to the database lock. The following endpoints will be summarized using the Safety Population:

- **Caregiver-recorded respiration rate**: Caregiver-recorded respiration rates will be presented using descriptive statistics at each time point for each USL261-treated seizure cluster episode. The number of subjects who have < 8 breaths per minute and > 24 breaths per minute after study drug administration will be presented by time point.

- **Requirement for unscheduled ER or EMS visit:** The proportion of subjects requiring an unscheduled ER or EMS visit within 24 hours after study drug administration will be summarized for each successive seizure cluster episode.
- **Adverse Events:** AE verbatim text will be coded using MedDRA and summarized by System Organ Class (SOC) and Preferred Term. Treatment-emergent AEs will be defined as those AEs that begin on or after study drug administration and up to 30 days after the last dose of study drug in the open-label study, or increase in severity on or after study drug administration.

  Subjects who experience at least one TEAE or SAE will be presented for each SOC and Preferred Term. Summaries of TEAEs will also be provided by severity and relationship to study drug. Treatment emergent adverse events will also be tabulated by age group (<18, ≥ 18 - <65 years, ≥65 years). Serious AEs and AEs leading to discontinuation will be summarized.

  Adverse events that occur within 30 days prior to the first study drug administration in the open-label study will be identified in the listings but will not be summarized.
- **Clinical Laboratory Data:** Clinical laboratory results for serum chemistry, hematology, and urinalysis will be presented by visit using summary statistics. Changes from baseline

will also be displayed. Normal range shift tables will be generated for selected parameters. In addition, clinically significant abnormalities, as predefined in the SAP, will be tabulated.

- **Vital Signs Measurements:** Vital sign measurements performed by study site staff will be presented using descriptive statistics. Systolic and diastolic BP (millimeters of mercury [mm Hg]), HR (beats per minute), respiration rate (breaths per minute), and temperature (degrees Celsius [°C]) will be summarized at each visit. Changes from baseline will also be displayed.
- **Physical, Nasal, and Neurological Examinations:** For physical, neurological, and nasal examinations the number and percent of subjects with normal and abnormal results (clinically significant vs. not clinically significant) for each body system or assessment will be presented for each visit.
- **C-SSRS:** C-SSRS results will be summarized at each visit. The number and percentage of subjects with each suicidal behavior and ideation will be displayed. The number and percentage of subjects with any suicidal behavior and any suicidal ideation, along with the number and percentage of subjects with at least 1 occurrence of suicidal behavior or ideation, will be calculated. In addition, the number of suicidal behaviors of each type (attempts, aborted attempts, and interrupted attempts) will be presented. Scores for suicidal ideation severity will be calculated for each type of ideation, and the total score will be summarized.
- **B-SIT:** For olfactory examination, the B-SIT scores and changes from baseline will be presented and plotted by visits. Further analysis adjusted by exposure and time may be conducted. Details will be included in the SAP.

10.5.2 Efficacy Analyses

The following endpoints will be analyzed using the Efficacy Evaluable Population:

Treatment Success: Treatment Success is a composite measure of efficacy that is defined as achieving both of the following criteria:

- Termination of seizure(s) within 10 minutes after study drug administration, and
- No recurrence of seizure beginning 10 minutes after study drug administration to 6 hours after study drug administration.

Subjects who receive the second open-label dose of USL261 within 6 hours of the first dose will not meet the definition of treatment success.

Treatment Success is a repeated efficacy measurement at every seizure cluster episode. All subjects included in the Efficacy Evaluable Population will be fitted into a generalized linear mixed model with appropriate link function and time-trend coefficients to study the short and long-term efficacy effect of USL261. This model will be able to address the data dependency within-subject and at the same time estimate subject-specific differences in the propensity to respond over time. Descriptive statistics will also be presented.

Time to return to baseline functionality (as determined by the caregiver): Time to return to baseline functionality after study drug administration will be summarized using Kaplan-Meier analysis for each successive seizure episode. Censoring rules will be described in detail in the SAP.

10.5.3 Exploratory Analyses

The following exploratory endpoints will be analyzed using the Efficacy Evaluable Population if there is sufficient evaluable data. The methods of analysis will be described in detail in the SAP.

- Proportion of subjects with recurrence of seizure(s) beginning 10 minutes after study drug administration to 4 hours after study drug administration.
- Time to next seizure with a start time >10 minutes after study drug administration.
- Proportion of subjects with recurrence of seizure(s) beginning 10 minutes after study drug administration to 24 hours after study drug administration.
- Time from administration of the first open-label dose of study drug to the second open-label dose of study.

10.5.4 Outcomes Analyses

The following questionnaires will be summarized using the Safety Population:

SF-12v2 Health Survey (SF-12v2): The eight domains of the SF-12 will be summarized at Visit 1 and the Final Visit or ET using descriptive statistics. The change from Visit 1 to the Final/ET Visit will also be presented.

Treatment Satisfaction Questionnaire for Medication (TSQM): The TSQM responses will be summarized by visit.

Intranasal Therapy Impact Questionnaire (ITIQ): Responses to the 2 questions of the ITIQ will be summarized for both patients and caregivers by visit.

Caregiver Questionnaire: Caregiver demographics will be summarized using descriptive statistics, counts, and percentages as appropriate.

10.5.5 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) constituted for the P261-401 study will have access to the data from this study for informational purposes and as supportive data during their review of the P261-401 study.

Details of the DSMB membership, meeting schedule, and data review and analysis will be documented in the DSMB Charter for the P261-401 study.

10.6 Sample Size Justification

Since enrollment is limited to subjects who have participated in Study P261-401, a maximum of 240 subjects (the planned number of subjects completing the Comparative Phase in P261-401) are expected to enroll in the study.

The subjects enrolled in this study will be a subset of the subjects participating in the P261-401 study. Thus, the sample size will depend on the number of subjects who participate from

P261-401 and is not based on any statistical calculation.

11 ADMINISTRATIVE PROCEDURES

11.1 Regulatory Approval

This study requires application to the appropriate regulatory authorities in the countries concerned. The study will only be undertaken following receipt of written approval or acknowledgement of receipt (depending on local regulation) from the regulatory authorities by USL, or following submission to appropriate authorities, whichever is required by the respective countries.

This study requires authorization by any member state Regulatory Authority where the clinical study will be conducted in accordance with National law requirements. The study will only be undertaken by USL following receipt of written approval from the Regulatory Authority.

This protocol will be submitted to the US FDA under Investigational New Drug (IND) Application No. 77,421 prior to study initiation.

11.2 Institutional Review Board or Independent Ethics Committee Approval

Before implementing this study, the study protocol, the proposed informed consent and assent forms, and other study materials will be approved or favorably reviewed by a properly constituted IRB / IEC.

USL or its designee must receive signed and dated written confirmation that the study protocol and ICF have been approved or favorably reviewed by the IRB/IEC before the study site will be initiated. The IRB / IEC Membership Roster (or assurance number, if applicable) must also be supplied to USL or its designee prior to site initiation.

Any amendment(s) to the study protocol that affect the study design, study procedures, or risk to study subjects, and any corresponding change to the informed consent or assent forms, must be approved by the IRB / IEC before the change is implemented, in conformance with GCP. If any such changes are made to the informed consent or assent forms, subjects and/or caregivers that

are still active in the study will be re-consented using the new form(s).

11.3 Study Personnel

The investigator should maintain a list of appropriately qualified persons who are delegated to perform significant study-related duties. In addition, the investigator should maintain a signature sheet to document signatures, initials, and study responsibilities of all persons authorized to make entries and/or corrections to the eCRF.

11.4 Ongoing Information for Independent Ethics Committee

Unless otherwise instructed by the IRB / IEC, the investigator or designee must submit to the IRB / IEC at a minimum:

- Information on SAEs from the investigator's site, as soon as possible.
- Expedited safety reports from the sponsor or its representatives, as soon as possible.
- Periodic or annual reports on the progress of the study.

11.5 Completion of Electronic Case Report Forms

The investigator is responsible for the accuracy and quality of the data recorded for this study. These recorded data should be a complete and accurate account of each subject's record collected during the study. Subject data that are collected may be substantiated by 2 types of source documents at the study center, paper and electronic (electronic source data is defined as electronic information not directly entered into the EDC system). Source data collected electronically or via paper will be entered onto the eCRFs in the EDC system. The Subject Workbook completed by the caregiver is considered a source document. The eCRFs will be completed according to guidelines provided by USL or its designee.

Access to the EDC system will be granted to trained and authorized study personnel only, and user identifications (IDs) and passwords must not be shared with other individuals. Only staff designated by the principal investigator on the Delegation of Authority form in the study file notebook will be eligible to enter or make edits to the data. Qualified research personnel will

accurately enter data from both study center- and subject / caregiver-generated source documents into the eCRFs provided for this study. Data will be entered into the eCRF shortly after each subject's visit. Study center personnel will exercise due diligence to ensure that study data are entered accurately and in their entirety from the study center's source documents into the appropriate data fields.

The investigator must review all data entries on a regular basis for completeness and accuracy. When changes or corrections are made to existing entries in the EDC system, the reason for the change must be clearly delineated. The investigator agrees to transfer study data into the EDC system in a timely fashion and to make the records available to the study monitor for full inspection. In addition, data queries should be answered promptly.

Although the study eCRF is the primary database for the study, all data entered into the eCRF must be recorded in the source documents, and any missing data must be explained. Source data will be retained by the study center as described in Section 11.12, Records of Study.

At the end of the study, by electronically signing the eCRFs, the investigator is attesting to his/her responsibility for the quality of all data recorded, as well as attesting that the data represent a complete and accurate record of each subject's participation in the study.

11.6 Study Monitoring

USL, as sponsor of this study, is responsible to regulatory authorities for ensuring the proper conduct of the study as regards to protocol adherence and validity of the data recorded on the eCRFs presented to the regulatory authorities. USL (or designated CRO [inVentiv Health Clinical]) has assigned study monitors and medical monitors to this study. Their duties are to aid the investigator and at the same time, USL, in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, a monitor will explain and ensure the investigator's understanding of all applicable regulations concerning the clinical evaluation of a pharmaceutical product (whether licensed or unlicensed), and ensure an understanding of the protocol, reporting responsibilities, and the validity of the data.

In order to perform their role well, the monitors must be given direct access to primary subject data that support data on the eCRFs for the study (e.g., Subject Workbooks, hospital and general practice charts, appointment books, original laboratory records). The investigator must make available such records to USL, designated CRO, quality assurance, IRB, and regulatory personnel for inspection and copying. Because this enters into the realm of subject confidentiality, this fact must be included in the information signed by the subject.

The investigator should agree, as a minimum requirement, to record the following information in the subject notes:

- Protocol identification number
- Date that the subject gave written informed consent
- All visit dates
- All AEs
- All concomitant medications

Entries in the subject notes must contain the signature or initials of the person making the entries.

The study monitor will perform source data verification at each monitoring visit.

11.7 Quality Assurance Procedures

Quality assurance activities include monitoring and source data verification by the study monitor. It is possible that USL Compliance Audit Unit personnel or their agents may audit the study center(s).

11.7.1 Access to Source Documentation

Source data are all original records of clinical findings, observations, or other activities in a clinical study, which are necessary to achieve study objectives and protect subject safety.

Source data are contained in source documents. Examples of these original documents and data records include the following:

- Hospital records.
- Clinical and office charts.
- Laboratory notes.
- Memoranda.
- Subjects' workbooks, diaries, or evaluation checklists.
- Pharmacy dispensing records.
- Recorded data from automated instruments.
- Copies or transcriptions certified after verification as being accurate and complete.
- X-rays, microfiches, photographic negatives, microfilm, or magnetic media.
- Subject files, including records kept at the pharmacy, laboratories, and at medico-technical departments involved in the clinical study.

Source documents are the originals of any document used by the investigator or hospital / institution that allows verification of the existence of the subject and substantiates the integrity of data collected during the trial. Source documents will be available to support all data recorded in the eCRF, unless this is otherwise specified in the eCRF. The investigator must allow designated representatives of the sponsor and regulatory inspectors to have direct access to the source documents to verify the data reported in the eCRFs.

The investigator must maintain source documents for each subject in the study, including source documents that are generated by the subject. All information in the eCRFs must be traceable to these source documents, which are generally maintained in the subject's file. The source documents should contain all demographic and medical information as well as a copy of the ICFs provided by subject and caregiver.

11.7.2 Auditing Procedures

The investigator will permit USL, USL representatives (designated CRO [inVentiv Health Clinical] and/or other designee), and regulatory authorities to conduct inspections during the study or after study completion. If a regulatory authority requests an inspection, the investigator must immediately inform USL (or CRO) of the request.

11.8 USL Policy on Fraud in Clinical Studies

In accordance with GCP, it is USL's policy always to investigate suspected cases of fraud.

11.9 Use of Information and Publication

It is intended that the results of the study may be published in the scientific literature. Results may also be used in submissions to regulatory authorities. The following conditions are to protect commercial confidential materials (e.g., patents), not to restrict publication.

All information concerning the drug currently under study, USL operations (such as patent applications, formula, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by USL and not previously published) is considered confidential by USL and shall remain the sole property of USL. The investigator agrees not to use it for other purposes without USL written consent.

It is understood by the investigator that USL will use the information developed in this clinical study in connection with the development of the drug currently under study and, therefore, this information may be disclosed as required to other USL investigators or any appropriate regulatory authorities. To allow for the use of information derived from this clinical study, the investigators understand that they have an obligation to obtain all necessary authorizations from study subjects in order to provide USL with complete test results and all data developed during this study.

A manuscript or abstract should not be submitted for publication or presentation until a New Drug Application is approved by the US FDA or permission is granted in writing by USL. In accordance with generally recognized principles of scientific collaboration, co-authorship with USL personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

Following completion of the study, the data may be considered for reporting at a scientific meeting(s) or for publication in a scientific journal. For specific information regarding

publications of this study, refer to the signed agreement between USL and the investigator.

Results of this study may also be used in submissions to regulatory authorities.

11.10 Amendment to Protocol

Approval of a protocol amendment by the investigator's IRB must be obtained before implementation, with the following exceptions:

- When necessary to eliminate apparent immediate hazard to the subject.
- When the change involves logistical or administrative aspects of the study.

The protocol amendment must be signed and dated by both USL and the investigator. USL will submit protocol amendments to the appropriate regulatory authorities (if required)/ Ethics Committee (if required) and notify other investigators using this protocol.

11.11 Deviations from Protocol

Deviations from a written protocol for individual subjects are inherent to clinical research and are categorized by USL as departures from protocol. A departure from protocol is a deviation of such magnitude as to affect whether the data can be evaluated for the subject or to potentially compromise the statistical analysis. Examples of deviations include the following:

- Violation of inclusion/exclusion criteria.
- Error in study drug randomization.
- Administration of an excluded concomitant medication during the course of the study.

The IRB / IEC will be informed of protocol deviations in a timely manner that is consistent with their requirements.

If the same protocol deviation occurs for multiple subjects, it must be recorded separately for each subject.

The investigator should contact USL or designee if continuing the subjects in the study is in

question as a result of the protocol deviation.

11.12 Records of Study

The investigator will retain essential study documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, USL261. Examples of essential documents include the following:

- IRB / IEC correspondence indicating approval / favorable opinion for the study protocol, ICFs, and all amendments to either of these documents.
- All source documents and laboratory records
- Informed consent forms signed by the subject or his/her LAR, and by the subject's caregiver.
- When applicable, subject assent forms.
- Completed Form FDA 1572.
- Statement of investigator.

If required by the applicable regulatory requirements or by an agreement with USL, these documents should be retained for a longer period (approximately 15 years). In the event that the investigator has a change of address or is planning to transfer these documents to another investigator's possession, the investigator must notify USL of such change.

11.13 Completion of Study

It is agreed that USL may terminate this study before the expiration of the agreed time period, provided a written notice is submitted a reasonable time in advance of intended termination.

11.14 Study Funding

The costs necessary to perform the study will be agreed with the investigator and/or the

management of the study facility and will be documented in a separate financial agreement that will be signed by the investigator and USL.

11.15 Financial Disclosure

Clinical investigators are required to provide financial disclosure information to allow the sponsor (USL) to submit the complete and accurate certification or financial disclosure statements to FDA as required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects. The term "clinical investigator" also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

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Appendix 1. Prohibited Concomitant Substances

The medications listed below are prohibited from Visit 1 through the Final Visit or ET Visit. If the subject was taking any of these medications at or before Visit 1, the time between the last dose of that substance and when the subject receives the study materials kit must be equal to or greater than the minimum washout time shown below.

The **first listing (Listing 1)** of substances represents **inhibitors or inducers of the cytochrome P450 3A family of enzymes**, and may alter the PK of midazolam. Food or beverage substances are shown in italic font; drugs, herbals, or nutritional supplements are shown in regular font.

The **second listing (Listing 2)** of substances represents **opioids, other respiratory depressants or other sedating medications**.

The following substances are prohibited when administered orally, by injection, or any other method intended for systemic delivery. Usage of topical, intravaginal, or ophthalmic formulations containing prohibited substances is allowable provided that such the usage is unlikely to achieve meaningful systemic levels. **Listing 1 and Listing 2 may not be all-inclusive**; any questions should be directed to the Medical Monitor.

Listing 1. Inhibitors or Inducers of Cytochrome P450 3A Family of Enzymes

	Generic or Substance Name	Other Name (US Brand Name or Research Designation	Minimum Washout Period (days)
A	Amiodarone	Cordarone, Nexterone	710 (24 months)
	Aprepitant	Emend	7
B	Boceprevir	Victrelis	7
C	Chloramphenicol	Alficetyn, Amphicol, Biomicin, Chlornitromycin, Chloromycetin Brochlor, Golden Eye, Optrex, Oftan Chlora, Phenicol, Medicom, Nevimycin Vernacetin, Veticol	7
	Cisapride	Propulsid	7
	Clarithromycin	Biaxin, Biaxin XL	7
D	Danazol	Danocrine	7

	Generic or Substance Name	Other Name (US Brand Name or Research Designation	Minimum Washout Period (days)
	Delavirdine	Rescriptor	7
	Diethyldithio-carbamate (diethyldione, Diethyldithio-carbamic acid)	—	7
E	Efavirenz	Efavirenz	11
G	Gestodene	Minesse	7
I	Imatinib	Gleevec	7
	Indinavir	Crixiban	7
	Itraconazole	Sporanox	7
K	Ketoconazole	Nizoral	7
L	Lopinavir	Kaletra, Aluvia	7
M	Mibefradil	Posicor (withdrawn from US market)	7
	Oral Miconazole[a]	Oravig	7
	Mifepristone	Mifeprex	7
N	Nefazodone	Serzone	7
	Nelfinavir	Viracept	7
	Nevirapine	Viramune	9
P	Posaconazole	Noxafil, Posanol	10
Q	Quinidine	Quin-Release, Quinaglute Dura-Tabs, Quinidex Extentabs	7
R	Rifabutin	Mycobutin	13
	Rifampin	Rifadin	7
	Ritonavir	Kaletra, Norvir	7
S	Saquinavir	Fortovase, Invirase	7
	Star fruit	—	7
	St. John's Wort	—	7
T	Tacrolimus	FK506, Prograf	8
	Telithromycin	Ketek	7
	Thalidomide	Thalomid	7
	Troleandomycin	Tao	7

	Generic or Substance Name	Other Name (US Brand Name or Research Designation	Minimum Washout Period (days)
V	Voriconazole	VFEND	7
Z	Zafirlukast	Accolate	7

[a] Topical and vaginal miconazole are allowed.

Listing 2. Opioids or other Respiratory Depressants

	Generic or Substance Name	Other Name (US Brand Name or Research Designation)	Minimum Washout Period (days)
Opiate Agonist			
A	Alfentanil	Alfenta	1
C	Codeine		1
F	Fentanyl	Fentora, Duragesic	1 (for acute intravenous) 7 (any other route)
H	Hydrocodone	Lorcet	1
	Hydromorphone	Dilaudid	1
L	Levorphanol	Levo-Dromoran	2
M	Methadone	Dolophine	2
	Meperidine	Demerol	1
	Morphine	Duramorph	1 (for acute intravenous) 7 (any other route)
O	Oxycodone	Oxycontin	1
	Oxymorphone	Numorphan	1
P	Propoxyphene	Darvon	7
S	Sufentanil	Sufenta	1
T	Tramodol	Ultram	1
Opiate Agonist-antagonist or Partial Agonists			
B	Buprenorphine	Buprenex	1
	Butorphanol	Stadol	7
N	Nalbuphine	Nubain	1
P	Pentazocine	Talwin NX	1
Other Sedating Medications			

	Generic or Substance Name	Other Name (US Brand Name or Research Designation)	Minimum Washout Period (days)
B	Buspirone	Ansial, Ansiced, Anxiron, Axoren, Bespar, BuSpar, Buspimen, Buspinol, Buspisal, Narol, Spitomin, Sorbon	7
P	Pimozide	Orap 15	15
	Propofol	Diprivan	1 (infusions ≤ 10 hours) 7 (infusions >10 hours)
T	Tetrahydrocanna-binol	Marinol, Dronabinol, marijuana	7

Appendix 2. Midazolam Injection, USP, Package Insert (Hospira)

Midazolam Injection, USP Rx only

WARNING

Adult and Pediatric: Intravenous midazolam has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam should be used only in hospital or ambulatory care settings, including physicians' and dental offices, that provide for continuous monitoring of respiratory and cardiac function, ie, pulse oximetry. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured (see ***WARNINGS***). For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedures.

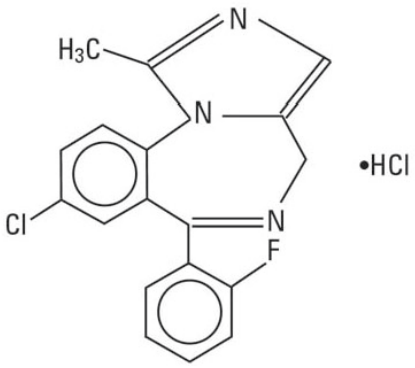
The initial intravenous dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system (CNS) depressants. The initial dose and all subsequent doses should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Doses of sedative medications in pediatric patients must be calculated on a mg/kg basis, and initial doses and all subsequent doses should always be titrated slowly. The initial pediatric dose of midazolam for sedation/anxiolysis/amnesia is age, procedure, and route dependent (see ***DOSAGE AND ADMINISTRATION*** for complete dosing information).

Neonates: Midazolam should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly with concomitant use of fentanyl (see ***DOSAGE AND ADMINISTRATION*** for complete information).

DESCRIPTION

Midazolam hydrochloride is a water-soluble benzodiazepine available as a sterile, nonpyrogenic parenteral dosage form for intravenous or intramuscular injection. Each mL contains midazolam hydrochloride equivalent to 1 mg or 5 mg midazolam compounded [redacted]

Midazolam is a white to light yellow crystalline compound, insoluble in water. The hydrochloride salt of midazolam, which is formed *in situ*, is soluble in aqueous solutions. Chemically, midazolam HCl is 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-a][1,4]benzodiazepine hydrochloride. Midazolam hydrochloride has the chemical formula $C_{18}H_{13}ClFN_3 \cdot HCl$, a calculated molecular weight of 362.24 and the following structural formula:



CLINICAL PHARMACOLOGY

Midazolam is a short-acting benzodiazepine central nervous system (CNS) depressant.

The effects of midazolam on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications. Onset time of sedative effects after IM administration in adults is 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. In one adult study, when tested the following day, 73% of the patients who received midazolam intramuscularly had no recall of memory cards shown 30 minutes following drug administration; 40% had no recall of the memory cards shown 60 minutes following drug administration. Onset time of sedative effects in the pediatric population begins within 5 minutes and peaks at 15 to 30 minutes depending upon the dose administered. In pediatric patients, up to 85% had no recall of pictures shown after receiving intramuscular midazolam compared with 5% of the placebo controls.

Sedation in adult and pediatric patients is achieved within 3 to 5 minutes after intravenous (IV) injection; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent of the adult patients in endoscopy studies had no recall of introduction of the endoscope; 82% of the patients had no recall of withdrawal of the endoscope. In one study of pediatric patients undergoing lumbar puncture or bone marrow aspiration, 88% of patients had impaired recall vs 9% of the placebo controls. In another pediatric oncology study, 91% of midazolam treated patients were amnestic compared with 35% of patients who had received fentanyl alone.

When midazolam is given IV as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or other sedative premedication. Some impairment in a test of memory was noted in 90% of the patients studied. A dose response study of pediatric patients premedicated with 1 mg/kg intramuscular (IM) meperidine found that only 4 out of 6 pediatric patients who received 600 mcg/kg IV midazolam lost consciousness, with eye closing at 108 ±140 seconds. This group was compared with pediatric patients who were given thiopental 5 mg/kg IV; 6 out of 6 closed their eyes at 20 ± 3.2 seconds. Midazolam did not dependably induce anesthesia at this dose despite concomitant opioid administration in pediatric patients.

Midazolam, used as directed, does not delay awakening from general anesthesia in adults. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline Trieger competency) usually indicate recovery within 2 hours but recovery may take up to 6 hours in some cases. When compared with patients who received thiopental, patients who received midazolam generally recovered at a slightly slower rate. Recovery from anesthesia or sedation for procedures in pediatric patients depends on the dose of midazolam administered, coadministration of other medications causing CNS depression and duration of the procedure.

In patients without intracranial lesions, induction of general anesthesia with IV midazolam is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that observed following IV thiopental. Preliminary data in neurosurgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with midazolam and with thiopental during intubation. No similar studies have been reported in pediatric patients.

The usual recommended intramuscular premedicating doses of midazolam do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent in adults. Intravenous induction doses of midazolam depress the ventilatory response to carbon dioxide stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental in adults. Impairment of ventilatory response to carbon dioxide is more marked in adult patients with chronic obstructive pulmonary disease (COPD). Sedation with IV midazolam does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (V_{max}) increase. In one study of pediatric patients under general anesthesia, intramuscular midazolam (100 or 200 mcg/kg) was shown to depress the response to carbon dioxide in a dose-related manner.

In cardiac hemodynamic studies in adults, IV induction of general anesthesia with midazolam was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 85/minute) tended to slow slightly. In pediatric patients, a comparison of IV midazolam (500 mcg/kg) with propofol (2.5 mg/kg) revealed a mean 15% decrease in systolic blood pressure in patients who had received IV midazolam vs a mean 25% decrease in systolic blood pressure following propofol.

Pharmacokinetics:

Midazolam's activity is primarily due to the parent drug. Elimination of the parent drug takes place via hepatic metabolism of midazolam to hydroxylated metabolites that are conjugated and excreted in the urine. Six single-dose pharmacokinetic studies involving healthy adults yield pharmacokinetic parameters for midazolam in the following ranges: volume of distribution (Vd), 1.0 to 3.1 L/kg; elimination half-life, 1.8 to 6.4 hours (mean approximately 3 hours); total clearance (Cl), 0.25 to 0.54 L/hr/kg. In a parallel group study, there was no difference in the clearance, in subjects administered 0.15 mg/kg (n=4) and 0.3 mg/kg (n=4) IV doses indicating linear kinetics. The clearance was successively reduced by approximately 30% at doses of 0.45 mg/kg (n=4) and 0.6 mg/kg (n=5) indicating non-linear kinetics in this dose range.

Absorption: The absolute bioavailability of the intramuscular route was greater than 90% in a cross-over study in which healthy subjects (n=17) were administered a 7.5 mg IV or IM dose. The mean peak concentration (C_{max}) and time to peak (T_{max}) following the IM dose was 90 ng/mL (20% cv) and 0.5 hr (50% cv). C_{max} for the 1-hydroxy metabolite following the IM dose was 8 ng/mL (T_{max}=1.0 hr).

Following IM administration, C_{max} for midazolam and its 1-hydroxy metabolite were approximately one-half of those achieved after intravenous injection.

Distribution: The volume of distribution (Vd) determined from six single-dose pharmacokinetic studies involving healthy adults ranged from 1.0-3.1 L/kg. Female gender, old age, and obesity are associated with increased values of midazolam Vd. In humans, midazolam has been shown to cross the placenta and enter into fetal circulation and has been detected in human milk and CSF (see ***CLINICAL PHARMACOLOGY*, Special Populations**).

In adults and children older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin.

Metabolism: In vitro studies with human liver microsomes indicate that the biotransformation of midazolam is mediated by cytochrome P450-3A4. This cytochrome also appears to be present in gastrointestinal tract mucosa as well as liver. Sixty to seventy percent of the biotransformation products is 1-hydroxy-midazolam (also termed alpha-hydroxymidazolam) while 4-hydroxy-midazolam constitutes 5% or less. Small amounts of a dihydroxy derivative have also been detected but not quantified. The principal urinary excretion products are glucuronide conjugates of the hydroxylated derivatives.

Drugs that inhibit the activity of cytochrome P450-3A4 may inhibit midazolam clearance and elevate steady-state midazolam concentrations.

Studies of the intravenous administration of 1-hydroxy-midazolam in humans suggest that 1-hydroxy-midazolam is at least as potent as the parent compound and may contribute to the net pharmacologic activity of midazolam. *In vitro* studies have demonstrated that the affinities of 1- and 4-hydroxy-midazolam for the benzodiazepine receptor are approximately 20% and 7%, respectively, relative to midazolam.

Excretion: Clearance of midazolam is reduced in association with old age, congestive heart failure, liver disease (cirrhosis) or conditions which diminish cardiac output and hepatic blood flow.

The principal urinary excretion product is 1-hydroxy-midazolam in the form of a glucuronide conjugate; smaller amounts of the glucuronide conjugates of 4-hydroxy- and dihydroxy-midazolam are detected as well. The amount of midazolam excreted unchanged in the urine after a single IV dose is less than 0.5% (n=5). Following a single IV infusion in 5 healthy volunteers, 45% to 57% of the dose was excreted in the urine as 1-hydroxymethyl midazolam conjugate.

Pharmacokinetics-continuous infusion: The pharmacokinetic profile of midazolam following continuous infusion, based on 282 adult subjects, has been shown to be similar to that following single-dose administration for subjects of comparable age, gender, body habitus and health status. However, midazolam can accumulate in peripheral tissues with continuous infusion. The effects of accumulation are greater after long-term infusions than after short-term infusions. The effects of accumulation can be reduced by maintaining the lowest midazolam infusion rate that produces satisfactory sedation.

Infrequent hypotensive episodes have occurred during continuous infusion; however, neither the time to onset nor the duration of the episode appeared to be related to plasma concentrations of midazolam or alpha-hydroxy-midazolam. Further, there does not appear to be an increased chance of occurrence of a hypotensive episode with increased loading doses.

Patients with renal impairment may have longer elimination half-lives for midazolam (see ***CLINICAL PHARMACOLOGY*, Special Populations: Renal Failure**).

Special Populations:

Changes in the pharmacokinetic profile of midazolam due to drug interactions, physiological variables, etc., may result in changes in the plasma concentration-time profile and pharmacological response to midazolam in these patients. For example, patients with acute renal failure appear to have a longer elimination half-life for midazolam and may experience delayed recovery (see ***CLINICAL PHARMACOLOGY*, Special Populations: Renal Failure**). In other groups, the relationship between prolonged half-life and duration of effect has not been established.

Pediatrics and Neonates: In pediatric patients aged 1 year and older, the pharmacokinetic properties following a single dose of midazolam reported in 10 separate studies of midazolam are similar to those in adults. Weight-normalized clearance is similar or higher (0.19 to 0.80 L/hr/kg) than in adults and the terminal elimination half-life (0.78 to 3.3 hours) is similar to or shorter than in adults. The pharmacokinetic properties during and following continuous intravenous infusion in pediatric patients in the operating room as an adjunct to general anesthesia and in the intensive care environment are similar to those in adults.

In seriously ill neonates, however, the terminal elimination half-life of midazolam is substantially prolonged (6.5 to 12.0 hours) and the clearance reduced (0.07 to 0.12 L/hr/kg) compared to healthy adults

or other groups of pediatric patients. It cannot be determined if these differences are due to age, immature organ function or metabolic pathways, underlying illness or debility.

Obese: In a study comparing normals (n=20) and obese patients (n=20) the mean half-life was greater in the obese group (5.9 vs 2.3 hrs). This was due to an increase of approximately 50% in the Vd corrected for total body weight. The clearance was not significantly different between groups.

Geriatric: In three parallel group studies, the pharmacokinetics of midazolam administered IV or IM were compared in young (mean age 29, n=52) and healthy elderly subjects (mean age 73, n=53). Plasma half-life was approximately two-fold higher in the elderly. The mean Vd based on total body weight increased consistently between 15% to 100% in the elderly. The mean Cl decreased approximately 25% in the elderly in two studies and was similar to that of the younger patients in the other.

Congestive Heart Failure: In patients suffering from congestive heart failure, there appeared to be a two-fold increase in the elimination half-life, a 25% decrease in the plasma clearance and a 40% increase in the volume of distribution of midazolam.

Hepatic Insufficiency: Midazolam pharmacokinetics were studied after an IV single dose (0.075 mg/kg) was administered to 7 patients with biopsy proven alcoholic cirrhosis and 8 control patients. The mean half-life of midazolam increased 2.5-fold in the alcoholic patients. Clearance was reduced by 50% and the Vd increased by 20%. In another study in 21 male patients with cirrhosis, without ascites and with normal kidney function as determined by creatinine clearance, no changes in the pharmacokinetics of midazolam or 1-hydroxy-midazolam were observed when compared to healthy individuals.

Renal Failure: Patients with renal impairment may have longer elimination half-lives for midazolam and its metabolites which may result in slower recovery.

Midazolam and 1-hydroxy-midazolam pharmacokinetics in 6 ICU patients who developed acute renal failure (ARF) were compared with a normal renal function control group. Midazolam was administered as an infusion (5 to 15 mg/hr). Midazolam clearance was reduced (1.9 vs 2.8 mL/min/kg) and the half-life was prolonged (7.6 vs 13 hr) in the ARF patients. The renal clearance of the 1-hydroxy-midazolam glucuronide was prolonged in the ARF group (4 vs 136 mL/min) and the half-life was prolonged (12 hr vs >25 hr). Plasma levels accumulated in all ARF patients to about ten times that of the parent drug. The relationship between accumulating metabolite levels and prolonged sedation is unclear.

In a study of chronic renal failure patients (n=15) receiving a single IV dose, there was a two-fold increase in the clearance and volume of distribution but the half-life remained unchanged. Metabolite levels were not studied.

Plasma Concentration-Effect Relationship: Concentration-effect relationships (after an IV dose) have been demonstrated for a variety of pharmacodynamic measures (eg, reaction time, eye movement, sedation) and are associated with extensive intersubject variability. Logistic regression analysis of sedation scores and steady-state plasma concentration indicated that at plasma concentrations greater than 100 ng/mL there was at least a 50% probability that patients would be sedated, but respond to verbal commands (sedation score = 3). At 200 ng/mL there was at least a 50% probability that patients would be asleep, but respond to glabellar tap (sedation score = 4).

Drug Interactions: For information concerning pharmacokinetic drug interactions with midazolam, see ***PRECAUTIONS***.

INDICATIONS AND USAGE

Midazolam injection is indicated:

- intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia;
- intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants;

- intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia);
- continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

Midazolam is associated with a high incidence of partial or complete impairment of recall for the next several hours (see ***CLINICAL PHARMACOLOGY***).

CONTRAINDICATIONS

Injectable midazolam is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma. Benzodiazepines may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam; patients with glaucoma have not been studied.

Midazolam is not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form.

WARNINGS

Midazolam must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression. Prior to the intravenous administration of midazolam in any dose, the immediate availability of oxygen, resuscitative drugs, age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, or apnea, i.e., pulse oximetry. Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures are taken immediately. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. Because intravenous midazolam depresses respiration (see ***CLINICAL PHARMACOLOGY***) and because opioid agonists and other sedatives can add to this depression, midazolam should be administered as an induction agent only by a person trained in general anesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway and supporting ventilation. **When used for sedation/anxiolysis/amnesia, midazolam should always be titrated slowly in adult or pediatric patients.** Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid intravenous administration should also be avoided in this population. See ***DOSAGE AND ADMINISTRATION*** for complete information.

Serious cardiorespiratory adverse events have occurred after administration of midazolam. These have included respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death or permanent neurologic injury. There have also been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations particularly in adult or pediatric patients with hemodynamic instability. Hypotension occurred more frequently in the sedation studies in patients premedicated with a narcotic.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported in both adult and pediatric patients. These reactions may be due to inadequate or excessive dosing or improper administration of midazolam; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. Should such reactions occur, the response to each dose of midazolam and all other drugs,

including local anesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in pediatric patients.

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premeditation also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk adult and pediatric surgical patients, elderly patients and debilitated adult and pediatric patients require lower dosages, whether or not concomitant sedating medications have been administered. Adult or pediatric patients with COPD are unusually sensitive to the respiratory depressant effect of midazolam. Pediatric and adult patients undergoing procedures involving the upper airway such as upper endoscopy or dental care, are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction. Adult and pediatric patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly (see ***CLINICAL PHARMACOLOGY***). Because elderly patients frequently have inefficient function of one or more organ systems and because dosage requirements have been shown to decrease with age, reduced initial dosage of midazolam is recommended, and the possibility of profound and/or prolonged effect should be considered.

Injectable midazolam should not be administered to adult or pediatric patients in shock or coma, or in acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of intravenous midazolam in adult or pediatric patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

There have been limited reports of intra-arterial injection of midazolam. Adverse events have included local reactions, as well as isolated reports of seizure activity in which no clear causal relationship was established. Precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

The safety and efficacy of midazolam following nonintravenous and nonintramuscular routes of administration have not been established. Midazolam should only be administered intramuscularly or intravenously.

The decision as to when patients who have received injectable midazolam, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of midazolam (see ***CLINICAL PHARMACOLOGY***) cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until one full day after anesthesia and surgery, whichever is longer. For pediatric patients, particular care should be taken to assure safe ambulation.

Usage in Pregnancy: **An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.**

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see ***DRUG ABUSE AND DEPENDENCE*** section).

Usage In Preterm Infants And Neonates: Rapid injection should be avoided in the neonatal population. Midazolam administered rapidly as an intravenous injection (less than 2 minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid intravenous injection of fentanyl. Seizures have been reported in several neonates following rapid intravenous administration.

The neonate also has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of midazolam.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including midazolam) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of midazolam for preterm and term infants includes amounts of benzyl alcohol well below that associated with toxicity; however, the amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources.

PRECAUTIONS

General: Intravenous doses of midazolam should be decreased for elderly and for debilitated patients (see *WARNINGS* and *DOSAGE AND ADMINISTRATION*). These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia.

Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Use with Other CNS Depressants: The efficacy and safety of midazolam in clinical use are functions of the dose administered, the clinical status of the individual patient, and the use of concomitant medications capable of depressing the CNS. Anticipated effects range from mild sedation to deep levels of sedation virtually equivalent to a state of general anesthesia where the patient may require external support of vital functions. Care must be taken to individualize and carefully titrate the dose of midazolam to the patient's underlying medical/surgical conditions, administer to the desired effect being certain to wait an adequate time for peak CNS effects of both midazolam and concomitant medications, and have the personnel and size-appropriate equipment and facilities available for monitoring and intervention (see **Boxed WARNING,** *WARNINGS* and *DOSAGE AND ADMINISTRATION* sections). Practitioners administering midazolam must have the skills necessary to manage reasonably foreseeable adverse effects, particularly skills in airway management. For information regarding withdrawal see *DRUG ABUSE AND DEPENDENCE* section.

Information for Patients: To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, especially blood pressure medication and antibiotics, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.
4. Patients should be informed of the pharmacological effects of midazolam, such as sedation and amnesia, which in some patients may be profound. The decision as to when patients who have received injectable midazolam, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized.
5. Patients receiving continuous infusion of midazolam in critical care settings over an extended period of time, may experience symptoms of withdrawal following abrupt discontinuation.

Drug Interactions: The sedative effect of intravenous midazolam is accentuated by any concomitantly administered medication, which depresses the central nervous system, particularly narcotics (e.g., morphine, meperidine and fentanyl) and also secobarbital and droperidol. Consequently, the dosage of

midazolam should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response (see ***DOSAGE AND ADMINISTRATION***).

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450-3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. These drug interactions may result in prolonged sedation due to a decrease in plasma clearance of midazolam.

The effect of single oral doses of 800 mg cimetidine and 300 mg ranitidine on steady-state concentrations of midazolam was examined in a randomized crossover study (n=8). Cimetidine increased the mean midazolam steady-state concentration from 57 to 71 ng/mL. Ranitidine increased the mean steady-state concentration to 62 ng/mL. No change in choice reaction time or sedation index was detected after dosing with the H2 receptor antagonists.

In a placebo-controlled study, erythromycin administered as a 500 mg dose, tid, for 1 week (n=6), reduced the clearance of midazolam following a single 0.5 mg/kg IV dose. The half-life was approximately doubled.

Caution is advised when midazolam is administered to patients receiving erythromycin since this may result in a decrease in the plasma clearance of midazolam.

The effects of diltiazem (60 mg tid) and verapamil (80 mg tid) on the pharmacokinetics and pharmacodynamics of midazolam were investigated in a three-way crossover study (n=9). The half-life of midazolam increased from 5 to 7 hours when midazolam was taken in conjunction with verapamil or diltiazem. No interaction was observed in healthy subjects between midazolam and nifedipine.

In a placebo-controlled study, saquinavir administered as a 1200 mg dose, tid, for 5 days (n=12), a 56% reduction in the clearance of midazolam following a single 0.05 mg/kg IV dose was observed. The half-life was approximately doubled.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular midazolam for premedication in adults.

The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of midazolam administered; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

Although the possibility of minor interactive effects has not been fully studied, midazolam and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration in adults. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of succinylcholine. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of midazolam.

Drug/Laboratory Test Interactions: Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* Midazolam maleate was administered with diet in mice and rats for 2 years at dosages of 1, 9 and 80 mg/kg/day. In female mice in

the highest dose group there was a marked increase in the incidence of hepatic tumors. In high-dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (25 times a human dose of 0.35 mg/kg) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.
Mutagenesis: Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes or in the micronucleus test in mice.
Impairment of Fertility: A reproduction study in male and female rats did not show any impairment of fertility at dosages up to 10 times the human IV dose of 0.35 mg/kg.
Pregnancy: Teratogenic Effects: Pregnancy Category D (see ***WARNINGS***).
Segment II teratology studies, performed with midazolam maleate injectable in rabbits and rats at 5 and 10 times the human dose of 0.35 mg/kg, did not show evidence of teratogenicity.
Nonteratogenic Effects: Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested were approximately 10 times the human dose of 0.35 mg/kg.
Labor and Delivery: In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following intramuscular administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.

The use of injectable midazolam in obstetrics has not been evaluated in clinical studies. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, midazolam is not recommended for obstetrical use.
Nursing Mothers: Midazolam is excreted in human milk. Caution should be exercised when midazolam is administered to a nursing woman.
Pediatric Use: The safety and efficacy of midazolam for sedation/anxiolysis/amnesia following single dose intramuscular administration, intravenously by intermittent injections and continuous infusion have been established in pediatric and neonatal patients. For specific safety monitoring and dosage guidelines see **Boxed WARNING, *CLINICAL PHARMACOLOGY*, *INDICATIONS AND USAGE*, *WARNINGS*, *PRECAUTIONS*, *ADVERSE REACTIONS*, *OVERDOSAGE*** and ***DOSAGE AND ADMINISTRATION*** sections. UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than do adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require closer monitoring. In obese PEDIATRIC PATIENTS, the dose should be calculated based on ideal body weight. When midazolam is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

Midazolam should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly, with concomitant use of fentanyl.
Geriatric Use: Because geriatric patients may have altered drug distribution and diminished hepatic and/or renal function, reduced doses of midazolam are recommended. Intravenous and intramuscular midazolam should be decreased for elderly and for debilitated patients (see ***WARNINGS*** and ***DOSAGE AND ADMINISTRATION***) and subjects over 70 years of age may be particularly sensitive. These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia. Administration of IM and IV midazolam to elderly and/or high risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous

system depressants capable of depressing respiration, especially narcotics (see ***DOSAGE AND ADMINISTRATION***).

Specific dosing and monitoring guidelines for geriatric patients are provided in the ***DOSAGE AND ADMINISTRATION*** section for premedicated patients for sedation/anxiolysis/amnesia following IV and IM administration, for induction of anesthesia following IV administration and for continuous infusion.

ADVERSE REACTIONS

See *WARNINGS* concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs were the most frequently seen findings following parenteral administration of midazolam in adults and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. The majority of serious adverse effects, particularly those associated with oxygenation and ventilation, have been reported when midazolam is administered with other medications capable of depressing the central nervous system. **The incidence of such events is higher in patients undergoing procedures involving the airway without the protective effect of an endotracheal tube, e.g., upper endoscopy and dental procedures.**

Adults: The following additional adverse reactions were reported after intramuscular administration:

headache (1.3%)	*Local effects at IM Injection site*
	pain (3.7%)
	induration (0.5%)
	redness (0.5%)
	muscle stiffness (0.3%)

Administration of IM midazolam to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics (see ***DOSAGE AND ADMINISTRATION***).

The following additional adverse reactions were reported subsequent to intravenous administration as a single sedative/anxiolytic/amnestic agent in adult patients:

hiccoughs (3.9%)	*Local effects at the IV site*
nausea (2.8%)	tenderness (5.6%)
vomiting (2.6%)	pain during injection (5.0%)
coughing (1.3%)	redness (2.6%)
"oversedation" (1.6%)	induration (1.7%)
headache (1.5%)	phlebitis (0.4%)
drowsiness (1.2%)	

Pediatric Patients: The following adverse events related to the use of IV midazolam in pediatric patients were reported in the medical literature: desaturation 4.6%, apnea 2.8%, hypotension 2.7%, paradoxical reactions 2.0%, hiccough 1.2 %, seizure-like activity 1.1% and nystagmus 1.1%. The majority of airway-related events occurred in patients receiving other CNS depressing medications and in patients where midazolam was not used as a single sedating agent.

Neonates: For information concerning hypotensive episodes and seizures following the administration of midazolam to neonates, see **Boxed WARNING,** ***CONTRAINDICATIONS***, ***WARNINGS*** and ***PRECAUTIONS*** sections.

Other adverse experiences, observed mainly following IV injection as a single sedative/anxiolytic/amnesia agent and occurring at an incidence of <1.0% in adult and pediatric patients, are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea
Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm
Gastrointestinal: Acid taste, excessive salivation, retching
CNS/Neuromuscular: Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia
Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness
Integumentary: Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site
Hypersensitivity: Allergic reactions including anaphylactoid reactions, hives, rash, pruritus
Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma

DRUG ABUSE AND DEPENDENCE

Midazolam is subject to Schedule IV control under the Controlled Substances Act of 1970.

Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs.

Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, hallucinations, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuation of benzodiazepines, including midazolam. Abdominal distention, nausea, vomiting, and tachycardia are prominent symptoms of withdrawal in infants. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. There is no consensus in the medical literature regarding tapering schedules; therefore, practitioners are advised to individualize therapy to meet patient's needs. In some case reports, patients who have had severe withdrawal reactions due to abrupt discontinuation of high-dose long-term midazolam, have been successfully weaned off of midazolam over a period of several days.

OVERDOSAGE

The manifestations of midazolam overdosage reported are similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity from midazolam overdosage has been reported.
Treatment of Overdosage: Treatment of injectable midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation, including administration of oxygen. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other

appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of midazolam overdosage.

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. There are anecdotal reports of reversal of adverse hemodynamic responses associated with midazolam following administration of flumazenil to pediatric patients. Prior to the administration of flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. **Flumazenil will only reverse benzodiazepine-induced effects but will not reverse the effects of other concomitant medications.** The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients. **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

Midazolam injection is a potent sedative agent that requires slow administration and individualization of dosage. Clinical experience has shown midazolam to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM MIDAZOLAM INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excessive single doses or rapid intravenous administration may result in respiratory depression, airway obstruction and/or arrest. The potential for these latter effects is increased in debilitated patients, those receiving concomitant medications capable of depressing the CNS, and patients without an endotracheal tube but undergoing a procedure involving the upper airway such as endoscopy or dental (see Boxed WARNING and *WARNINGS*).

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported in adult and pediatric patients. Should such reactions occur, caution should be exercised before continuing administration of midazolam (see ***WARNINGS***).

Midazolam injection should only be administered IM or IV (see ***WARNINGS***).

Care should be taken to avoid intra-arterial injection or extravasation (see ***WARNINGS***).

Midazolam Injection may be mixed in the same syringe with the following frequently used premedications: morphine sulfate, meperidine, atropine sulfate or scopolamine. Midazolam, at a concentration of 0.5 mg/mL, is compatible with 5% dextrose in water and 0.9% sodium chloride for up to 24 hours and with lactated Ringer's solution for up to 4 hours. Both the 1 mg/mL and 5 mg/mL formulations of midazolam may be diluted with 0.9% sodium chloride or 5% dextrose in water.

Monitoring: Patient response to sedative agents, and resultant respiratory status, is variable. Regardless of the intended level of sedation or route of administration, sedation is a continuum; a patient may move easily from light to deep sedation, with potential loss of protective reflexes. This is especially true in pediatric patients. Sedative doses should be individually titrated, taking into account patient age, clinical status and concomitant use of other CNS depressants. Continuous monitoring of respiratory and cardiac function is required (i.e., pulse oximetry).

Adults and Pediatrics: Sedation guidelines recommend a careful presedation history to determine how a patient's underlying medical conditions or concomitant medications might affect their response to

sedation/analgesia as well as a physical examination including a focused examination of the airway for abnormalities. Further recommendations include appropriate presedation fasting.

Titration to effect with multiple small doses is essential for safe administration. It should be noted that adequate time to achieve peak central nervous system effect (3 to 5 minutes) for midazolam should be allowed between doses to minimize the potential for oversedation. Sufficient time must elapse between doses of concomitant sedative medications to allow the effect of each dose to be assessed before subsequent drug administration. This is an important consideration for all patients who receive intravenous midazolam.

Immediate availability of resuscitative drugs and *age-* and *size-appropriate* equipment and personnel trained in their use and skilled in airway management should be assured (see ***WARNINGS***).

Pediatrics: For deeply sedated pediatric patients a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Intravenous access is not thought to be necessary for all pediatric patients sedated for a diagnostic or therapeutic procedure because in some cases the difficulty of gaining IV access would defeat the purpose of sedating the child; rather, emphasis should be placed upon having the intravenous equipment available and a practitioner skilled in establishing vascular access in pediatric patients immediately available.

USUAL ADULT DOSE

INTRAMUSCULARLY

For preoperative sedation/anxiolysis/amnesia (induction of sleepiness or drowsiness and relief of apprehension and to impair memory of perioperative events).	The recommended premedication dose of midazolam for good risk (ASA Physical Status I & II) adult patients below the age of 60 years is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM) administered up to 1 hour before surgery.
For intramuscular use, midazolam should be injected deep in a large muscle mass.	The dose must be individualized and reduced when IM midazolam is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant narcotics or other CNS depressants (see ***ADVERSE REACTIONS***). In a study of patients 60 years or older, who did not receive concomitant administration of narcotics, 2 to 3 mg (0.02 to 0.05 mg/kg) of midazolam produced adequate sedation during the preoperative period. The dose of 1 mg IM midazolam may suffice for some older patients if the anticipated intensity and duration of sedation is less critical. As with any potential respiratory depressant, these patients require observation for signs of cardiorespiratory depression after receiving IM midazolam.
	Onset is within 15 minutes, peaking at 30 to 60 minutes. It can be administered concomitantly with atropine sulfate or scopolamine and reduced doses of narcotics.

INTRAVENOUSLY

Sedation/anxiolysis/amnesia for procedures (See ***INDICATIONS AND USAGE***): Narcotic premedication results in less variability in patient response and a reduction in dosage of midazolam. For peroral procedures, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.	When used for sedation/anxiolysis/amnesia for a procedure, dosage must be individualized and titrated. Midazolam should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. Individual response will vary with age, physical status and concomitant medications, but may also vary independent of these factors. (See ***WARNINGS*** concerning cardiac/respiratory arrest/airway obstruction/hypoventilation.)

Premedicated Patients: When the patient has received sedative or narcotic premedication, particularly narcotic premedication, the range of recommended doses is 0.15 to 0.35 mg/kg.

In average adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice.

The initial dose of 0.2 mg/kg is recommended for good risk (ASA I & II) surgical patients over the age of 55 years.

In some patients with severe systemic disease or debilitation, as little as 0.15 mg/kg may suffice.

Narcotic premedication frequently used during clinical trials included fentanyl (1.5 to 2 mcg/kg IV, administered 5 minutes before induction), morphine (dosage individualized, up to 0.15 mg/kg IM), and meperidine (dosage individualized, up to 1 mg/kg IM). Sedative premedications were hydroxyzine pamoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for intravenous fentanyl, administered 5 minutes before induction, all other premedications should be administered approximately 1 hour prior to the time anticipated for midazolam induction.

Injectable midazolam can also be used during maintenance of anesthesia, for surgical procedures, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases.

Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.

CONTINUOUS INFUSION

For continuous infusion, midazolam 5 mg/mL formulation is recommended diluted to a concentration of 0.5 mg/mL with 0.9% sodium chloride or 5% dextrose in water.

Usual Adult Dose: If a loading dose is necessary to rapidly initiate sedation, 0.01 to 0.05 mg/kg (approximately 0.5 to 4 mg for a typical adult) may be given slowly or infused over several minutes. This dose may be repeated at 10 to 15 minute intervals until adequate sedation is achieved. For maintenance of sedation, the usual initial infusion rate is 0.02 to 0.1 mg/kg/hr (1 to 7 mg/hr). Higher loading or maintenance infusion rates may occasionally be required in some patients. The lowest recommended doses should be used in patients with residual effects from anesthetic drugs, or in those concurrently receiving other sedatives or opioids.

Individual response to midazolam is variable. The infusion rate should be titrated to the desired level of sedation, taking into account the patient's age, clinical status and current medications. In general, midazolam should be infused at the lowest rate that produces the desired level of sedation. Assessment of sedation should be performed at regular intervals and the midazolam infusion rate adjusted up or down by 25% to 50% of the initial infusion rate so as to assure adequate titration of sedation level. Larger adjustments or even a small incremental dose may be necessary if rapid changes in the level of sedation are indicated. In addition, the infusion rate should be decreased by 10% to 25% every few hours to find the minimum effective infusion rate. Finding the minimum effective infusion rate decreases the potential accumulation of midazolam and provides for the most rapid recovery once the infusion is terminated. Patients who exhibit agitation, hypertension, or tachycardia in response to noxious stimulation, but who are otherwise adequately sedated, may benefit from concurrent administration of an opioid analgesic. Addition of an opioid will generally reduce the minimum effective midazolam infusion rate.

PEDIATRIC PATIENTS

UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than do adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require close monitoring (see tables below). In obese PEDIATRIC PATIENTS, the dose should be calculated based on ideal body weight. When midazolam is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. For appropriate patient monitoring, see **Boxed WARNING,** *WARNINGS*, and *DOSAGE AND ADMINISTRATION*, *MONITORING*. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (OAA/S)

Assessment Categories				
Responsiveness	**Speech**	**Facial Expression**	**Eyes**	**Composite Score**
Responds readily to name spoken in normal tone	normal	normal	clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	mild slowing or thickening	mild relaxation	glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	slurring or prominent slowing	marked relaxation (slack jaw)	glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	few recognizable words	—	—	2
Does not respond to mild prodding or shaking	—	—	—	1 (deep sleep)

FREQUENCY OF OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION COMPOSITE SCORES IN ONE STUDY OF CHILDREN UNDERGOING PROCEDURES WITH INTRAVENOUS MIDAZOLAM FOR SEDATION

Age Range (years)	**n**	**OAA/S Score**				
		1 (deep sleep)	2	3	4	5 (alert)
1-2	16	6 (38%)	4 (25%)	3 (19%)	3 (19%)	0
>2-5	22	9 (41%)	5 (23%)	8 (36%)	0	0
>5-12	34	1 (3%)	6 (18%)	22 (65%)	5 (15%)	0
>12-17	18	0	4 (22%)	14 (78%)	0	0
Total (1-17)	90	16 (18%)	19 (21%)	47 (52%)	8 (9%)	0

INTRAMUSCULARLY

For sedation/anxiolysis/amnesia prior to anesthesia or for procedures, intramuscular midazolam can be used to sedate pediatric patients to facilitate less traumatic insertion of an intravenous catheter for titration of additional medication.

USUAL PEDIATRIC DOSE (NON-NEONATAL)

Sedation after intramuscular midazolam is age and dose dependent: higher doses may result in deeper and more prolonged sedation. Doses of 0.1 to 0.15 mg/kg are usually effective and do not prolong emergence from general anesthesia. For more anxious patients, doses up to 0.5 mg/kg have been used. Although not systematically studied, the total dose usually does not exceed 10 mg. If midazolam is given with an opioid, the initial dose of each must be reduced.

INTRAVENOUSLY BY INTERMITTENT INJECTION

For sedation/anxiolysis/amnesia prior to and during procedures or prior to anesthesia.

USUAL PEDIATRIC DOSE (NON-NEONATAL)

It should be recognized that the depth of sedation/anxiolysis needed for pediatric patients depends on the type of procedure to be performed. For example, simple light sedation/anxiolysis in the preoperative period is quite different from the deep sedation and analgesia required for an endoscopic procedure in a child. For this reason, there is a broad range of dosage. For all pediatric patients, regardless of the indications for sedation/anxiolysis, it is vital to titrate midazolam and other concomitant medications slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes. Since midazolam is water soluble, it takes approximately three times longer than diazepam to achieve peak EEG effects, therefore one must wait an additional 2 to 3 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. If other medications capable of depressing the CNS are coadministered, the peak effect of those concomitant medications must be considered and the dose of midazolam adjusted. The importance of drug titration to effect is vital to the safe sedation/anxiolysis of the pediatric patient. The total dose of midazolam will depend on patient response, the type and duration of the procedure, as well as the type and dose of concomitant medications.

1. *Pediatric patients less than 6 months of age:* Limited information is available in non-intubated pediatric patients less than 6 months of age. It is uncertain when the patient transfers from neonatal physiology to pediatric physiology, therefore the dosing recommendations are unclear. Pediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful monitoring are essential.
2. *Pediatric patients 6 months to 5 years of age:* Initial dose 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint but usually does not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
3. *Pediatric patients 6 to 12 years of age:* Initial dose 0.025 to 0.05 mg/kg; total dose up to 0.4 mg/kg may be needed to reach the desired endpoint but usually does not exceed 10 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
4. *Pediatric patients 12 to 16 years of age:* Should be dosed as adults. Prolonged sedation may be associated with higher doses; some patients in this age range will require higher than recommended adult doses but the total dose usually does not exceed 10 mg.

The dose of midazolam must be reduced in patients premedicated with opioid

	or other sedative agents including midazolam. Higher risk or debilitated patients may require lower dosages whether or not concomitant sedating medications have been administered (see *WARNINGS*).
CONTINUOUS INTRAVENOUS INFUSION	USUAL PEDIATRIC DOSE (NON-NEONATAL)
For sedation/anxiolysis/amnesia in critical care settings.	To initiate sedation, an intravenous loading dose of 0.05 to 0.2 mg/kg administered over at least 2 to 3 minutes can be used to establish the desired clinical effect IN PATIENTS WHOSE TRACHEA IS INTUBATED. (Midazolam should not be administered as a rapid intravenous dose.) This loading dose may be followed by a continuous intravenous infusion to maintain the effect. An infusion of midazolam injection has been used in patients whose trachea was intubated but who were allowed to breathe spontaneously. Assisted ventilation is recommended for pediatric patients who are receiving other central nervous system depressant medications such as opioids. Based on pharmacokinetic parameters and reported clinical experience, continuous intravenous infusions of midazolam should be initiated at a rate of 0.06 to 0.12 mg/kg/hr (1 to 2 mcg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental intravenous doses of midazolam can be administered to increase or maintain the desired effect. Frequent assessment at regular intervals using standard pain/sedation scales is recommended. Drug elimination may be delayed in patients receiving erythromycin and/or other P450-3A4 enzyme inhibitors (see ***PRECAUTIONS*, Drug Interactions** section) and in patients with liver dysfunction, low cardiac output (especially those requiring inotropic support), and in neonates. Hypotension may be observed in patients who are critically ill, particularly those receiving opioids and/or when midazolam is rapidly administered. When initiating an infusion with midazolam in hemodynamically compromised patients, the usual loading dose of midazolam should be titrated in small increments and the patient monitored for hemodynamic instability, e.g., hypotension. These patients are also vulnerable to the respiratory depressant effects of midazolam and require careful monitoring of respiratory rate and oxygen saturation.
CONTINUOUS INTRAVENOUS INFUSION	USUAL NEONATAL DOSE
For sedation in critical care settings.	Based on pharmacokinetic parameters and reported clinical experience in preterm and term neonates WHOSE TRACHEA WAS INTUBATED, continuous intravenous infusions of midazolam injection should be initiated at a rate of 0.03 mg/kg/hr (0.5 mcg/kg/min) in neonates <32 weeks and 0.06 mg/kg/hr (1 mcg/kg/min) in neonates >32 weeks. Intravenous loading doses should not be used in neonates, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. This is particularly important because of the potential for adverse effects related to metabolism of the benzyl alcohol (see ***WARNINGS*, Usage In Preterm Infants And Neonates**). Hypotension may be observed in patients who are critically ill and in preterm and term infants, particularly those receiving fentanyl and/or when midazolam is administered rapidly. Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm patients whose trachea is not intubated.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Package configurations containing midazolam hydrochloride equivalent to **1 mg** midazolam/**mL**:

NDC No.	Container Description	Fill Volume	Total Midazolam (per container)
0409-2587-05	Fliptop Vial	10 mL	10 mg

Package configurations containing midazolam hydrochloride equivalent to **5 mg** midazolam/**mL**:

NDC No.	Container Description	Fill Volume	Total Midazolam (per container)
0409-2596-03	Fliptop Vial	5 mL	25 mg
0409-2596-05	Fliptop Vial	10 mL	50 mg

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

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Appendix 3. Amendment 4

Protocol Number: P261-402

Protocol Title:

An Open-Label Safety Study of USL261 in the Outpatient Treatment of Subjects with Seizure Clusters

REASON FOR CHANGE TO PROTOCOL

Change 1

While the most common peripheral cause of dysosmia is olfactory neuron loss due to upper respiratory tract infection (URTI), nasal products have also been associated with smell disturbances. For example, Zicam Cold Remedy Nasal Gel and Swabs, was withdrawn from the U.S. market in 2009 due to long lasting or permanent loss of smell. The Brief Smell Identification Test (B-SIT) was added to assess the long-term effects of USL261 on olfaction.

Change 2

The introduction section was updated to reflect current study status.

SECTIONS OF PROTOCOL AFFECTED BY CHANGE

Change 1

Synopsis – Study Objective(s):

- **Brief Smell Identification Test (B-SIT)**

Synopsis – Safety Assessments:

Collection of AEs, physical, nasal and neurological examinations, clinical laboratory evaluations,

vital sign measurements, caregiver-recorded respiration rate, C-SSRS, ~~and~~ ER or EMS visits**, and B-SIT**.

Table 1 – Procedure Schedule:

Phase	Screening	Test-Dose Phase	Comparative Phase		
Visit Number	**1**	**2[a]**	**3[b]**	**Treatment[c]**	**4 or ET[d]**
Study Assessments					
B-SIT		**X**	**X**		**X**

2 STUDY OBJECTIVES

- **B-SIT**

6.1.2 Visit 2 through Visit X

- **Administer B-SIT (see Section 6.2.2.6)**

6.1.5 Final Visit or Early Termination Visit

- **Administer B-SIT (see Section 6.2.2.6)**

6.2.2.6 Brief Smell Identification Test (B-SIT)

The Brief Smell Identification Test (B-SIT) will be conducted to assess olfactory function. The B-SIT is a brief 12-item, self-administered microencapsulated odorant test for measuring olfactory function.

The B-SIT will be conducted at Visit 2 through X and the Final or ET Visit, except in cases where obtaining this information is not feasible or appropriate, as determined by the investigator. In addition, the B-SIT will be performed only if a validated version in the appropriate language is available.

10.5.1 Safety Analyses

- **B-SIT: For olfactory examination, the B-SIT scores and changes from baseline will be presented and plotted by visits. Further analysis adjusted by exposure and time may be conducted. Details will be included in the SAP.**

Change 2

1.3.1.3 Study P261-201

Study P261-201 was a single-center, in-patient trial investigating the safety, tolerability, PK, and PD of escalating single- and two-dose regimens of USL261 compared to placebo in adult subjects with epilepsy. Subjects were assigned sequentially to 1 of 4 cohorts to receive either USL261 (10.0 mg, 15.0 mg, 17.5 mg, or 20.0 mg) or placebo at two dosing visits separated by ≥ 3 days. Each subject received USL261 or placebo at Visit 2. At Visit 3, each subject received the same total dose as he/she received at Visit 2 administered as a divided dose. ~~The results of this study are pending.~~

USL261 was absorbed rapidly (approximately 9 minutes to 19 minutes after a single dose; approximately 19 to 22 minutes after the two-dose regimen). Following either single dose or repeat dose administration, PK parameters for both MZ and 1-OH MZ were similar across cohorts and did not exhibit dose dependent changes. Exposure to MZ and 1-OH MZ (as indicated by Cmax and AUC parameters) was not dose proportional following single dose or repeat dose administration of 10.0 mg to 20.0 mg. Effects of USL261 on sedation and psychomotor performance were transient following single and repeat dose administration and were consistent across USL261 doses. Consistent with PK results, no dose response was observed in SSS or OAA/S Sum and Composite scores or their corresponding PD parameters from 10.0 to 20.0 mg USL261 following either single or repeat dose administration.

USL261 was generally safe and well-tolerated following single- or repeat-dose administration up to the maximum evaluated total dose level of 20 mg in adult subjects with epilepsy taking concomitant AEDs. In total, 58 subjects (96.7%) reported 179 TEAEs. All of the reported

TEAEs were considered mild in severity with the majority (96.0%) were considered "probably related" to study drug. Treatment-emergent AEs reported in ≥20% of subjects in any group were nasal discomfort and throat irritation, which occurred in 96% of subjects administered MDZ NS. However, there was no clear dose relationship and these events also occurred frequently in placebo subjects. Nasal mucosal disorder, headache, dysgeusia, and hiccups were also common TEAEs, occurring in ≥10% MDZ NS subjects.

1.3.1.4 Study P261-102

Study P261-102 was a single-center trial investigating the safety, tolerability, PK, and PD of single 2.5 mg and 5.0 mg doses of USL261 in generally healthy geriatric and non-geriatric subjects. Enrollment was stratified into non-geriatric (18 – 40 years old, inclusive) and geriatric (≥ 65 years old) groups such that there were 12 subjects in the non-geriatric range and 18 subjects in the geriatric range. Subjects were randomly assigned to receive single doses of both 2.5 mg and 5.0 mg USL261 in a 2x2 crossover fashion with a washout period of 4 – 10 days between dosing. ~~Preliminary results indicate that although systemic exposures after administration of IN USL261 were approximately 20-45% higher in the geriatric group compared to non geriatric volunteers, maximum and overall sedation effect was comparable, and no increase in moderate or severe AEs was observed for the geriatric group.~~ **Mean systemic exposure (AUC) and peak plasma concentrations (Cmax) of MDZ were 20–45% higher in the geriatric subjects compared with nongeriatric subjects. Geriatric subjects exhibited greater cognitive effects than nongeriatric subjects, whereas maximum and overall sedation effects were comparable between the two groups.**

Of the 30 enrolled subjects, 26 subjects (87%) reported at least one TEAE during the study with more geriatric subjects reporting a TEAE than younger subjects. All reported TEAEs (n=115) were considered mild in severity; most (91.3%) were considered "probably related" to the study drug. No SAEs or deaths were reported, and no subject discontinued study participation due to a TEAE. Although there were some differences between the 2.5 mg and 5.0 mg doses with regard to the incidence of the more frequently reported AEs, there did not appear to be a consistent association with dose.

Protocol Signature Page

Authorized Sponsor Representative Signature:

[redacted] Pharm.D.

[redacted]
Date

Upsher-Smith Laboratories, Inc.
6701 Evenstad Drive
Maple Grove, MN 55369-6026

Investigator Agreement: By my signature, I confirm that my staff and I have carefully read and understand this protocol or protocol amendment, and agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by Upsher-Smith Laboratories, Inc. (USL). For protocol amendments, I agree not to implement the amendment without agreement from USL and prior submission to and written approval (where required) from the Institutional Review Board (IRB), except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements). I agree to conduct the study in accordance with International Conference of Harmonization (ICH) E6, Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements.

Principal Investigator

Name of Investigator (Print)

Study Center Number

Signature of Investigator

Date