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**Clinical Research Protocol**

**Protocol Title:** A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Intranasal Midazolam (USL261) in the Outpatient Treatment of Subjects with Seizure Clusters

**ARTEMIS-1: Acute Rescue Therapy in Epilepsy with Midazolam Intranasal Spray-1**

**Protocol Number:** P261-401

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## SYNOPSIS

<b>Sponsor:</b> Upsher-Smith Laboratories, Inc. (USL)
<b>Name of Development Product:</b> USL261 (intranasal midazolam; formerly ITI-111)
<b>Study Title:</b> A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Intranasal Midazolam (USL261) in the Outpatient Treatment of Subjects with Seizure Clusters
<b>Study Number:</b> P261-401
<b>Study Phase:</b> III
<b>Efficacy Objective(s):</b> <u>Primary Efficacy Objective:</u> To evaluate the efficacy of USL261 compared with that of intranasal (IN) placebo for the outpatient treatment of seizure clusters based on Treatment Success, which is defined as achieving both of the following: <ul style="list-style-type: none"><li>• Termination of seizure(s) within 10 minutes after study drug administration, and</li><li>• No recurrence of seizure(s) beginning 10 minutes after study drug administration to 6 hours after study drug administration</li></ul> <u>Secondary Efficacy Objective(s):</u> To evaluate the efficacy of USL261 compared with that of IN placebo for the outpatient treatment of seizure clusters using the following: <ul style="list-style-type: none"><li>• Proportion of subjects with recurrence of seizure(s) beginning 10 minutes after study drug administration to 4 hours after study drug administration</li><li>• Time to next seizure with a start time &gt; 10 minutes after study drug administration</li></ul>
<b>Safety Objective:</b> To evaluate the safety and tolerability of USL261 for the treatment of seizure clusters using the following assessments: <ul style="list-style-type: none"><li>• Adverse events (AEs)</li><li>• Caregiver-recorded respiration rate at 15 minutes, 30 minutes, 1 hour, 2 hours and 4 hours after study drug administration in the Comparative Phase</li><li>• Clinical laboratory tests</li><li>• Vital signs measurements (systolic and diastolic blood pressure, pulse rate, respiration rate and temperature) as recorded by the study center personnel</li><li>• Physical, nasal and neurological examinations</li><li>• Brief Smell Identification Test (B-SIT)</li><li>• Columbia-Suicide Severity Rating Scale (C-SSRS)</li><li>• Requirement for unscheduled emergency room (ER) or emergency medical service (EMS) visit within 24 hours after study drug administration</li></ul>
<b>Study Design:</b> This is a phase III multicenter study, with 2 distinct phases and 4 study center visits. The first phase is the Test-Dose Phase where subjects will receive 2 doses of open-label 5.0 mg USL261 administered 10 minutes apart at the study center. The Test-Dose Phase is designed to assess the safety, tolerability, and pharmacokinetics (PK) of USL261 in a monitored setting and provide the caregivers with training on the study procedures. The Test-Dose Phase will be followed by the Comparative Phase, an outpatient, double-blind, placebo-controlled, parallel-group phase. In the Comparative Phase, all subjects will be randomized 2:1 to receive 5.0 mg USL261 or placebo. During the Comparative Phase, the subject's caregiver will administer the double-blind study drug when the subject experiences a seizure cluster that meets the study criteria, as described in the subject's individualized Patient Management Plan (PMP). If the treated seizure cluster 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 < 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 Patient Management Plan), the double-blind dose of study medication may be

followed by a single dose of 5.0 mg USL261. Any time between 24 to 120 hours after study drug administration, subjects and caregivers will return to the study center for a post-dose study visit.

A maximum of approximately 350 subjects, aged 12 years or older, with a documented history of seizure clusters and on a stable antiepileptic drug (AED) regimen will be enrolled in the Test-Dose Phase. Before any subject continues to the Comparative Phase, safety data from at least 25 subjects in the Test-Dose Phase will be reviewed by an independent Data and Safety Monitoring Board (DSMB). Enrollment will temporarily halt once approximately 25 subjects complete the Test-Dose Phase, to allow the DSMB to review the safety data. If the safety data from this initial cohort supports continuation of the trial according to the DSMB, enrollment into the Test-Dose Phase will resume and the initial 25 subjects will proceed to the Comparative Phase. All subsequent subjects will progress directly from Test-Dose Phase to the Comparative Phase.

**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/Independent Ethics Committee policy
2. Subject has a competent, adult (age  $\geq 18$ ) caregiver(s) who is able to recognize and observe the subject's seizure cluster episodes, 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 is not likely to conceive, as indicated by a "yes" answer to at least 1 of the following questions:

- Is the subject a male?
- Is the subject a postmenopausal female with greater than 1 year since last menses and a follicular stimulating hormone value greater than 40 mIU/mL?
- Is the subject a female who has written medical documentation of being permanently sterilized (e.g. hysterectomy, double oophorectomy, bilateral salpingectomy)?
- 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:

- 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. Subject has an established diagnosis of partial or generalized epilepsy that includes **all** of the following:

- A documented history of seizure clusters lasting a minimum of 10 minutes from the time the seizure cluster is recognized
- The 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
- 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

- In the investigator's opinion, it would be safe for the subject to receive placebo as a first dose of study drug followed by active treatment (USL261) as the second dose of study drug no earlier than 10 minutes after the first dose
  - The subject's stereotyped seizure cluster pattern is composed of multiple ( $\geq 2$ ) partial or generalized seizures
  - The subject's stereotyped seizure cluster pattern was established  $> 3$  months before Visit 1
  - A frequency of  $\geq 3$  stereotyped seizure clusters during the year before Visit 1
  - At least 1 stereotyped seizure cluster occurring  $\leq 4$  months before Visit 1
  - The seizure cluster pattern described above is confirmed by a central reviewer
6. Subject is receiving a regimen of AED(s) that has been stable (i.e., no changes in the type of AED) since Visit 1 and for  $\geq 7$  days before Visit 2. Changes in dose of an AED are allowed during the study; however, the new dose level must be kept stable for at least 7 days before the subject receives study drug. Benzodiazepines that are used for rescue therapy of seizures or for non-epilepsy indications are allowed provided they are typically used  $\leq 3$  days within a 7-day period on average and always at the same dose. Daily use of a benzodiazepine as a chronic AED is not permitted.
7. Subject has had a documented brain computerized tomography or magnetic resonance imaging review, performed after diagnosis of epilepsy and before Visit 1, that confirms the absence of a progressive neurological disorder
8. Subject weight is 40 kg to 125 kg (inclusive)
9. Subject must have a screening (Visit 1) 12-lead electrocardiogram (ECG) that meets the following criteria:
- QTcF interval  $\leq 450$  msec for males and  $\leq 470$  msec for females
  - Consistent sinus rhythm as determined by the investigator
  - No left bundle branch block (LBBB)
  - No other clinically significant conduction disorders as determined by the investigator
10. Subject must have screening (Visit 1) vital sign values that meet the following criteria:
- Systolic blood pressure of  $\leq 160$  mm Hg
  - Diastolic blood pressure of  $\leq 90$  mm Hg
  - Pulse rate of 50 to 115 bpm, inclusive
  - No clinically significant vital sign values as determined by the investigator
- Note: At the discretion of the investigator, out-of-range blood pressure or heart rate measurements may be repeated once, and the repeat measurement used in relation to this inclusion.

#### Exclusions

##### At Visit 1 (Screening)

1. Subject has a neurological disorder that is likely to progress in the next year
2. Subject has acute narrow-angle glaucoma
3. 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
4. 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
5. Subject has had psychogenic, non-epileptic seizure(s) within the 5 years before Visit 1
6. Subject has suicidality, defined as any of the following: a) active suicidal plan/intent or active suicidal thoughts in the 6 months before Visit 1 as defined by a Columbia-Suicide Severity Rating Scale (C-SSRS) suicidal ideation score  $\geq 3$ , b) any suicide attempt in the past 5 years as determined by the C-SSRS or medical history, or c) other clinically significant suicidality as determined by the investigator
7. Subject, in the investigator's opinion, has met the criteria for a major depressive episode at any time within 6 months before Visit 1 (criteria defined by the current edition of the *Diagnostic and Statistical Manual of Mental Disorders*)
8. Subject has or has had psychosis in the 12 months before Visit 1, excluding postictal psychosis

9. Subject has a history of their stereotypical seizure cluster (for which they are being enrolled in the study) progressing to status epilepticus (as determined by the investigator) within the 2 years before Visit 1
10. Subject has a history of drug or alcohol abuse within 1 year before Visit 1
11. Subject has a positive pregnancy test at Visit 1 or is currently pregnant or breastfeeding (females only)
12. Subject has a history of allergy or any significant adverse reaction (including rash) to midazolam
13. Subject is currently using an investigational drug or device or has used such within 30 days before Visit 1
14. Subject is currently using a vagal nerve stimulator (VNS) unless the device has been implanted for at least 6 months and the settings have not changed within 4 weeks before Visit 1
15. Subject has plasma phenobarbital concentrations  $> 35 \mu\text{g/mL}$  at Visit 1 (phenobarbital concentration will be measured in subjects taking phenobarbital and in subjects for which the investigator deems it necessary)
16. Subject has any clinically significant laboratory abnormality as determined by the investigator and as confirmed by repeat testing, or has any of the following laboratory abnormalities at Visit 1 as confirmed by repeat testing:
  - Alanine transaminase (ALT) and/or aspartate transaminase (AST) results  $> 2$  times the upper limit of normal
  - White blood cell count  $< 2.5 \times 10^9/\text{L}$
  - Sodium  $< 128 \text{ mEq/L}$
  - Creatinine  $> 2.0 \text{ mg/dL}$
17. Subject is not appropriate for the study for any other reason as determined by the investigator

At Visit 2

18. Subject has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory abnormality, or required a new treatment or medication which meets any previously described study exclusion criteria.
19. Subject has a positive pregnancy test (females only)
20. Subject has active suicidal plan/intent or suicidal thoughts as defined by a C-SSRS suicidal ideation score  $\geq 3$  or has had a suicide attempt since the last visit
21. Subject has consumed any clinically significant CYP450 3A inhibitor/inducer, opioid, other respiratory depressant (excluding antiepileptic drugs) within the required washout period before Visit 2
22. Subject has any of the following during the observation period after administration of the USL261 test dose at Visit 2:
  - Blood pressure (BP)
    - Systolic blood pressure (SBP)  $< 85 \text{ mm Hg}$  and the change from baseline (pre-dose evaluation) in SBP is deemed clinically significant by the investigator
    - $\geq 40 \text{ mm Hg}$  decrease from baseline (pre-dose evaluation) in SBP
    - Diastolic blood pressure (DBP)  $< 50 \text{ mm Hg}$  and the change from baseline (pre-dose evaluation) in DBP is deemed clinically significant by the investigator
    - $\geq 30 \text{ mm Hg}$  decrease from baseline (pre-dose evaluation) in DBP
  - Heart rate (HR)
    - HR  $> 120$  or  $< 50$  beats per minute (bpm) and change from baseline (pre-dose evaluation) in HR is deemed clinically significant by the investigator
    - $\geq 40 \text{ bpm}$  change from baseline (pre-dose evaluation) in HR
  - Respiratory rate (RR)
    - RR  $> 24$  breaths per minute and change from baseline (pre-dose evaluation) in RR is deemed clinically significant by the investigator
    - RR  $< 8$  breaths per minute while awake or after arousing
  - Sedation to the degree that the subject does not respond to mild prodding or shaking
  - Oxygen saturation  $< 90\%$  for  $> 30$  seconds or requires oxygen at anytime
  - Clinically-significant ECG findings as determined by the investigator

Note: At the discretion of the investigator, out-of-range BP or HR measurements may be repeated once, and the repeat measurement used in relation to exclusion criteria, as long as the rules outlined in [Section 6.2.2.3](#) are followed.

At Visit 3

23. Subject has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory abnormality, or required a new treatment or medication which meets any previously described study exclusion criteria
24. Subject has a positive pregnancy test
25. Subject has active suicidal plan/intent or suicidal thoughts as defined by a C-SSRS suicidal ideation score  $\geq 3$  or has had a suicide attempt since the last visit.

**Study Population:** A maximum of approximately 350 subjects enrolled in the Test-Dose Phase in order to achieve 240 subjects completing the Comparative Phase. This assumes that approximately 32% of subjects enrolled in the Test-Dose Phase do not complete the Comparative Phase.

**Test/Reference Product, Dose, and Mode of Administration:**

**Test Product:** USL261 (intranasal midazolam; formerly ITI-111)

**Test-Dose Phase:** Two (2) open-label 5.0 mg doses (1 actuation each), separated by 10 minutes (total dose 10 mg)

**Comparative Phase:** One (1) double-blind 5.0 mg dose (1 actuation); One (1) 5.0 mg dose (1 actuation) administered for persistent or recurrent seizure activity

**Reference Product:** Placebo nasal spray

**Comparative Phase only:** One (1) double-blind dose (1 actuation)

**Duration of Treatment:** 10 minutes for Test-Dose Phase, variable for Comparative Phase

**Duration of Subject Participation:**

**Screening:** Up to 28 days; can be longer during the time of DSMB review

**Test-Dose Phase:** Up to 28 days; can be longer during the time of DSMB review

**Comparative Phase:** The duration of each subject's participation in the Comparative Phase will be variable and will be determined by the frequency of observed seizure events. Assuming an average of 3 seizure clusters per year, approximately half of the study subjects complete the study within ~4 months after randomization to treatment. Subjects may remain in the Comparative Phase for up to 6 months. Any subject who has not treated a seizure cluster meeting the study criteria within 6 months of Visit 3 (Randomization) will be discontinued from the study.

**Efficacy Assessment(s):**

Efficacy will be determined using the following information at a minimum:

- Date and time of study drug administration
- Date, start, and stop time of each seizure within 24 hours after any study drug administration
- Date and time when subject has returned to full baseline functionality after the treated seizure cluster, as determined by the caregiver

**Safety Assessments:**

Collection of AEs, physical and neurological examinations, clinical laboratory evaluations, vital signs, caregiver-recorded respiration rate, 12-Lead ECG, pulse oximetry, sedation (determined by the OAA/S), C-SSRS, the need for second dose of medication or emergency treatment, and B-SIT.

**Pharmacokinetic Assessments:**

Blood samples will be collected before and at 5, 10, 20, 30 minutes and 1, 2, and 4 hours after administration of the first 5.0 mg test dose of USL261 at Visit 2. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, blood samples will be collected before and at 5, 10, 20, 30 minutes and 1 hour after administration of the first 5.0 mg test dose of USL261 at Visit 2.

**Statistical Methods:**

**Efficacy**

Efficacy variables will be analyzed using the modified Intent-to-Treat (mITT) Population, which consists of all subjects who are randomized to receive double-blind treatment, who receive at least 1 dose of study drug during the Comparative Phase, and who have any post-treatment efficacy assessments.

Primary Efficacy Endpoint and Analysis:

The primary efficacy endpoint is the proportion of subjects who meet the criteria for Treatment Success. Treatment Success is a composite measure of efficacy that will be assessed based upon the first seizure cluster treated with study drug during the Comparative Phase. Treatment Success is defined as achieving the following:

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

The primary efficacy endpoint will be analyzed by Fisher's Exact Test. Chi-squared test will be performed as a sensitivity analysis.

The trial utilizes a group sequential design with 3 interim analyses and a maximum of approximately 240 subjects who have completed the Comparative Phase. Subjects who receive at least 1 dose of study drug during the Comparative Phase and who complete Visit 4 will have completed the Comparative Phase. The interim analyses will occur at N=132, 165, and 204 subjects complete the Comparative Phase with a final analysis (if needed) at N=240 subjects completing the Comparative Phase. At each interim analysis the trial may be stopped for efficacy or futility. Interim analyses for efficacy are evaluated using a Lan-DeMets alpha spending function approximating the Pocock boundary to preserve type I error at 2.5%. Futility monitoring is based on Bayesian predictive probabilities. At each interim analysis the trial is stopped for futility if the predictive probability of success at the maximal sample size is less than 10%. Assuming treatment rates of 0.40 for the placebo arm and Odds Ratio of 2.9, the power of this design is approximately 90%. These analyses will be conducted using the mITT population and a one-sided test comparing two populations. Interim analyses for efficacy and futility will be performed by an unblinded interim monitoring committee separate from the Sponsor.

Secondary Efficacy Endpoints and Analyses:

The secondary efficacy variables include the following:

- Proportion of subjects with recurrence of a seizure(s) beginning 10 minutes after administration of study drug to 4 hours after administration of study drug, by Fisher's Exact Test. In addition, Chi-squared test will be performed as a sensitivity analysis.
- Time to next seizure with a start time > 10 minutes after study drug administration, analyzed by a log-rank test, and presented with Kaplan-Meier estimates for time to event at specific percentiles

**Safety**

Safety analyses will be performed using the Safety Population, which includes all subjects that receive at least 1 dose of study drug. Safety data from both the Test-Dose Phase and the Comparative Phase will be summarized.

*Safety Endpoints*

- 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 treatment received and visit
- Vital sign measurements (SBP, DBP, HR, respiration rate and temperature) and oxygen saturation performed by study center staff will be summarized at each visit and time point
- Caregiver-recorded respiration rate from the Comparative Phase will be presented using descriptive statistics at each time point. 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.
- Changes from baseline in 12-lead ECG parameters in the Test Dose Phase will be summarized.
- The number of subjects requiring an unscheduled ER or EMS visit within 24 hours after study drug administration in the Comparative Phase will be analyzed by Fisher's Exact Test.
- Suicidal behavior and ideation using the C-SSRS will be summarized at each visit.
- OAA/S sum and composite scores after the study drug administration in the Test-Dose Phase will be presented by time point.

- Physical, nasal, and neurological examination results will be presented by treatment group and visit.
- Olfactory assessment results and changes from baseline will be presented by treatment group and visit.

**Pharmacokinetic**

*Pharmacokinetic Endpoints*

Pharmacokinetic (PK) profile of midazolam and 1-hydroxymidazolam will be assessed at the Test Dose Visit after administration USL261. The following PK parameters will be calculated:

- $AUC_{0-t}$  – the area under the plasma concentration-time curve from time 0 to last measurable concentration estimated by the linear trapezoidal method
- $AUC_{0-\infty}$  – the area under the plasma concentration-time curve from time zero extrapolated to infinity
- $C_{max}$  – the maximum plasma concentration
- $t_{max}$  – the time to maximum plasma concentration
- $\lambda_z$  – the terminal elimination rate constant
- $t_{1/2}$  – the terminal elimination half-life
- $t_{lag}$  – the time before the first measurable plasma concentration
- $CL/F$  – apparent clearance\*
- $V_{\beta}/F$  - volume of distribution\*

\* calculate for Midazolam only and not for 1-OH-midazolam.



**Table 1. Procedure Schedule**

Phase	Screening	Test-Dose Phase	Comparative Phase		
			Visit Number	1	2[a]
<b>Study Assessments</b>					
Informed consent[e]	X				
Register subject with IRT	X				
Inclusion/Exclusion evaluation	X	X	X		
Caregiver training[f]	X	X	X		
Demographics	X				
Medical/surgical history[g]	X				
Concomitant medication review	X	X	X		X
ER and EMS Visit Review [h]	X				X
Physical exam[i]	X	X	X		X
Neurological exam[j]	X	X	X		X
B-SIT		X	X		X
Clinical laboratory testing[k]	X				X
FSH level (females only)	X				
Pregnancy testing[l] (all females)	X	X	X		X
Drug screen[m]	X				
Patient Management Plan (PMP)[n]	X	X	X		
Central review of seizure cluster description[o]	X				
Treatment administration		X[p]		X	
Call central study nurse hotline [q]				X	
Pharmacokinetic blood sampling[r]		X			
Observer's Assessment of Alertness/Sedation (OAA/S)[s]		X			
12-lead ECG	X	X[t]			
Body weight	X	X	X		X
Height	X				X
Vital signs[u]	X	X	X		X
Caregiver-recorded respiration rate[v]		X		X	
Pulse oximetry[u]		X			
Report test dose information on IRT		X			
Columbia- Suicide Severity Rating Scale [w]	X	X	X		X
Outcome Assessments		X			X
Randomization using IRT			X		
Dispense study materials kit [x]			X		
Record seizure activity in Subject Workbook				X	
Evaluate subject's return to baseline functionality [y]				X	
Adverse event collection	X	X	X	X	X
Collect study drug containers, used and unused					X
Review/collect Subject Workbook					X

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Telephone follow-up		X[z]
<p>[a] Visit 2 assessments occurring at the same time should be completed in the following order: ECG, OAA/S, vitals, pulse oximetry, PK blood draw, and second dose; Visit 2 will occur within 28 days of Visit 1. If necessary, assessments may be performed up to 1 minute before or 1 minute after the scheduled time.</p> <p>[b] For patients enrolled in the study after the initial DSMB review, Visit 3 will occur a minimum of 24 hours and a maximum of 28 days after Visit 2.</p> <p>[c] These assessments will be performed by the caregiver.</p> <p>[d] Visit 4 will occur between 24 and 120 hours after double-blind study drug administration. Any subject who has not treated a seizure cluster meeting the study criteria within 6 months of Visit 3 (Randomization) will return to the study center for Visit 4 (Early Termination)..</p> <p>[e] Informed consent provided by subject (or subject's LAR) and caregiver before any other study-specific procedures; assent may also be required for some subjects (see <a href="#">Section 5</a>)</p> <p>[f] Caregiver training includes, but is not limited to, providing self-study training to the caregiver and review of that training by the study center personnel. It also includes CPR and airway management training for caregivers. For details on caregiver training, see <a href="#">Section 9.3.3</a>.</p> <p>[g] Includes seizure history and current/past medication use; complete at Visit 1 (see <a href="#">Section 6.2.2.1</a>).</p> <p>[h] At Visit 1, collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency in the year prior to screening. At Visit 4, 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. Number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since last visit or follow-up phone call will also be collected on each monthly telephone follow up call between Visit 3 and Visit 4 or ET.</p> <p>[i] Physical examination includes assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, and extremities, and a nasal cavity examination using a nasal speculum (see <a href="#">Section 6.2.2.2</a>).</p> <p>[j] A complete neurological examination will be performed at Visits 1 and 4/ET. A partial neurological examination will be performed at Visits 2 and 3 (see <a href="#">Section 6.2.2.2</a>).</p> <p>[k] Includes hematology, serum chemistry, and urinalysis; phenobarbital levels will be assessed at Visit 1 for subjects taking phenobarbital and in subjects for which the investigator deems it necessary (see <a href="#">Section 6.2.2.7</a>).</p> <p>[l] Serum pregnancy test at Visit 1, urine pregnancy tests at Visits 2, 3, and 4/ET (see <a href="#">Section 6.2.2.7</a>).</p> <p>[m] Includes barbiturates, benzodiazepines, cocaine, marijuana, methamphetamine, opiates, and phencyclidine (all in urine) and alcohol (blood) (see <a href="#">Section 6.2.2.7</a>).</p> <p>[n] PMP preparation begins at Visit 1. PMP should be completed before a subject receives the first test dose of USL261 at Visit 2. PMP provided to and reviewed with subject and caregiver at Visit 3 (see <a href="#">Section 9.3.1</a>).</p> <p>[o] Approval of each subject's seizure cluster pattern by central reviewer is required for study inclusion (see <a href="#">Section 9.3.1</a>)</p> <p>[p] At Visit 2, subjects will receive a test dose of 5.0 mg USL261 administered by a member of the study center personnel followed by a second dose of 5.0 mg USL261 10 minutes later administered by the caregiver under the supervision of study center personnel (see <a href="#">Section 6.1.7</a>).</p> <p>[q] Caregivers to call the central study nurse hotline as soon as possible after administering study drug.</p> <p>[r] Blood samples for PK assessment will be collected before and at 5, 10, 20, 30 minutes and 1, 2, and 4 hours after the first test dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, blood samples will be collected before and at 5, 10, 20, 30 minutes and 1 hour after administration of the first 5.0 mg test dose of USL261 at Visit 2.</p> <p>[s] At Visit 2, the OAA/S will be administered before and at 5, 10, 20, 30 minutes and 1, 2, and 4 hours after the first test dose by a trained member of the study center personnel (see <a href="#">Section 6.2.2.5</a>). After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, the OAA/S will be administered before and at 5, 10, 20, 30 minutes and 1 hour after the first test dose by a trained member of the study center personnel.</p> <p>[t] ECG will be performed twice at Visit 2: once before and once 15 minutes after the first test dose (see <a href="#">Section 6.2.2.4</a>)</p> <p>[u] Vital signs include blood pressure (BP), heart rate (HR), respiration rate (RR), and temperature. At Visit 2, BP, HR, RR, and pulse oximetry are recorded before and at 5, 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 3 and 4 hours after the first test dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, BP, HR, RR, and pulse oximetry will be recorded before and at 5, 10, 15, 20, 30, 45 minutes and 1 hour after the first test dose. Temperature will be measured only at the pre-dose time point.</p> <p>[v] Caregiver counts the number of breaths taken by the subject during a 30-second interval. At Visit 2, caregivers will measure respiration rate before and at 5, 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 3 and 4 hours after the first test dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, caregivers will measure respiration rate before and at 5, 10, 15, 20, 30, 45 minutes and 1 hour after the first test dose. On the day of treatment, caregivers will measure respiration rate at approximately 15 and 30 minutes and 1, 2, and 4 hours after study drug administration (see <a href="#">Section 6.2.2.3</a>).</p> <p>[w] Baseline/Screening version of the C-SSRS is administered at Visit 1. The Since Last Visit version is administered at Visits 2, 3 and 4/ET.</p> <p>[x] 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.</p> <p>[y] Caregiver will 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.</p>		

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[z] After Visit 3, telephone follow-up calls with the subject, subject's LAR, or subject's caregiver are to occur monthly until Visit 4 or ET.  
Abbreviations: BP = blood pressure; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; HR = heart rate; IRT = Interactive Response Technology System; LAR = legally acceptable representative; OAA/S = Observer's Assessment of Alertness/Sedation; PMP = patient management plan; QOL = quality of life; RR = respiration rate

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## LIST OF ABBREVIATIONS

Abbreviation	Definition
ACLS	Advanced Cardiac Life Support
AE	Adverse Event
AED	Antiepileptic drug
ALT	Alanine aminotransferase (same as SGPT)
AST	Aspartate aminotransferase (same as SGOT)
AUC <sub>0-t</sub>	Area under the plasma concentration-time curve from time 0 to time of last measureable concentration
AUC <sub>0-∞</sub>	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
β-hCG	Beta-human chorionic gonadotropin
bid	Twice daily dosing
BLQ	Below lower limit of quantification
BP	Blood pressure
bpm	Beats per minute
B-SIT	Brief Smell Identification Test
CFR	Code of Federal Regulations
CI	Confidence interval
C <sub>max</sub>	Maximum plasma concentration
CPR	Cardiopulmonary resuscitation
CRO	Clinical research organization
DBP	Diastolic blood pressure
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
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
GLP	Good Laboratory Practice
HR	Heart rate
ICH	International Conference on Harmonization
ICF	Informed consent form
IEC	Independent ethics committee
IM	Intramuscular
IN	Intranasal
Inc	Incorporated
IND	Investigational new drug
IRB	Institutional Review Board

<b>Abbreviation</b>	<b>Definition</b>
ITI	Ikano Therapeutics, Inc., study initiator
IV	Intravenous
IRT	Interactive Response Technology System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
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
PR	Rectal
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
T <sub>lag</sub>	Time before the first measurable plasma concentration
T <sub>max</sub>	Time to reach the maximum plasma concentration
T <sub>1/2</sub>	Terminal half-life
US	United States
USL	Upsher-Smith Laboratories, Inc., study sponsor
USL261	Intranasal midazolam, study drug (formally ITI-111)
USP	United States Pharmacopeia
VNS	Vagal nerve stimulator
WBC	White blood cell

## 1 INTRODUCTION

### 1.1 Background Information

Acute repetitive seizures and seizure clusters occur in a subset of epilepsy patients. Seizure clusters have distinguishable characteristics that are easily recognized by patients, caregivers, and physicians and include a consistent onset (auras, prodrome) that may be indicative of convulsive or non-convulsive symptoms. Although patients typically recover between seizures, these seizure can last anywhere from minutes to hours.[1] When a cluster of seizures occurs outside a hospital, the patient must often be transported to an acute care facility so medical personnel can administer intravenous (IV) therapy to stop the seizure(s).[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 seizure cessation and prevention of seizure recurrence.[1] Acute benzodiazepine treatment is effective for seizure control and often results in rapid seizure cluster termination; 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. While rectal diazepam gel (Diastat<sup>®</sup>, Valeant Pharmaceuticals International) is currently available in the United States (US), a portion of the population does not respond adequately to this treatment, and/or for some, the rectal route of administration is inappropriate or unacceptable.[7] As such, a treatment that is effective in interrupting seizure activity, has a rapid onset of action, and is easily administered in the outpatient setting is currently an unmet medical need.

Midazolam is a benzodiazepine with potent inhibitory activity at the GABA-A receptor and demonstrates anticonvulsant properties.[8] In adults, midazolam is usually administered via IV or intramuscularly (IM) at doses of 1 mg to 10 mg; pediatric patients are dosed by weight (mg/kg) and usually require higher doses than adults.[9] Like other benzodiazepines, midazolam administration may cause sedation, anxiolysis, and amnesia.[10, 11] Sedative

effects usually occur within 5 minutes of IV administration and within 15 minutes of 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 IN midazolam was originally described in the late 1980s,[10] and over the past 15 years, approximately 20 publications have described it as a safe and efficacious treatment for seizure control in a variety of populations, including adult and pediatric.[7, 10, 13-31] Publications such as these demonstrate the desire of patients, caregivers, and physicians to have this type of product available for acute intermittent treatment of seizure clusters. Furthermore, use of IN midazolam for treatment of seizures has been advocated by numerous 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 mg/mL) approved for IV delivery administered IN with a needleless syringe at doses  $\leq 0.6$  mg/kg. The delivery of IV-approved midazolam sterile injection solution intranasally has not been optimized, nor is it approved by the Food and Drug Administration (FDA). In fact, the volume of midazolam sterile injection solution usually ranges from 1 ml-2 mL,[11] which exceeds the recommended volume for optimal IN delivery ( $\leq 200$   $\mu$ L).[34] Despite the sub-optimal formulation and delivery system, IN delivery of midazolam sterile injection solution has been very effective in some 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 of

USL261 delivers adequate drug concentrations in a small volume (100 µL), and preliminary human studies show positive pharmacokinetic (PK) and bioavailability properties with good safety and tolerability. The present study is designed to establish the efficacy and safety of USL261 for the outpatient treatment of seizure clusters.

## 1.2 Non-Clinical 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 <sub>max</sub> 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	832
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	914
							Daily dose 2: 749	
				F	60	6.5	Daily dose 1: 770	803
							Daily dose 2: 918	
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<sub>max</sub>, maximum plasma concentration; NOAEL, no-observable-adverse-effect level.

[a] Number of animals/sex/group varied by treatment.

[b] C<sub>max</sub> at Day 13 is presented for WIL-637002 and WIL-637001; C<sub>max</sub> at Day 88 is presented for WIL-637003

[c] AUC<sub>last</sub> at Day 13 is presented for WIL-637002 and WIL-637001; Total AUC<sub>0-24</sub> 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)

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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 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 10-160). 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.

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
<i>Completed Studies</i>							
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 substest 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	
<b>Ongoing Studies</b>								
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  $\geq 10\%$  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  $\geq 3$  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  $\geq 10\%$  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  $\geq 3$  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  $\geq 20\%$  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  $\geq 10\%$  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 ( $\geq 65$  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.

## 2 STUDY OBJECTIVES

### 2.1 Efficacy Objectives

#### 2.1.1 Primary Efficacy Objective

To evaluate the efficacy of USL261 compared with that of IN placebo for the outpatient treatment of seizure clusters based on Treatment Success, which is defined as achieving both of the following:

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Upsher-Smith Laboratories, Inc.



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

### 2.1.2 Secondary Efficacy Objectives

To evaluate the efficacy of USL261 compared with that of IN placebo for the outpatient treatment of seizure clusters using the following:

- 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

### 2.1.3 Exploratory Efficacy Objectives

To evaluate the efficacy of USL261 for the outpatient treatment of seizure clusters using the following:

- Proportion of subjects with recurrence of seizure(s) beginning 10 minutes after study drug administration to 24 hours after study drug administration
- Time to return to full baseline functionality (as determined by the caregiver)
- Analyses for subjects receiving 2 doses of USL261 (see [Section 10.5.3.1](#))
- Subject and caregiver outcome assessments

## 2.2 Safety Objective

To evaluate the safety and tolerability of USL261 for the treatment of seizure clusters using the following assessments:

- AEs
- Caregiver-recorded respiration rate at 15 minutes, 30 minutes, 1 hour, 2 hours and 4 hours after study drug administration in the Comparative Phase
- Clinical laboratory tests

- Vital sign measurements (systolic and diastolic BP, HR, RR and temperature) as recorded by the study center personnel
- Physical, nasal and neurological examinations
- Brief Smell Identification Test (B-SIT)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Requirement for unscheduled ER or EMS visit within 24 hours after study drug administration

### 2.3 Pharmacokinetic Objective

To evaluate the PK profile of USL261 after administration of USL261 using the following PK parameters:

- $AUC_{0-t}$  – the area under the plasma concentration-time curve from time 0 to last measurable concentration estimated by the linear trapezoidal method
- $AUC_{0-\infty}$  – the AUC from time zero extrapolated to infinity
- $C_{max}$  – the maximum plasma concentration
- $t_{max}$  – the time to maximum plasma concentration
- $t_{1/2}$  – the terminal elimination half-life
- $\lambda_z$  – the terminal elimination rate constant
- $t_{lag}$  – the time before the first measurable plasma concentration
- $CL/F$  – apparent clearance
- $V_{\beta}/F$  – volume of distribution

## 3 DESCRIPTION OF STUDY

### 3.1 Overview

This is a phase III multicenter study, with 2 distinct phases and 4 study center visits as depicted in [Figure 1](#). The first phase is the Test-Dose Phase where subjects will receive 2 doses of open-label 5.0 mg USL261 administered 10 minutes apart at the study center. The Test-Dose Phase is designed to assess the safety, tolerability, and PK of USL261 in a monitored setting and provide the caregivers with training on the study procedures.

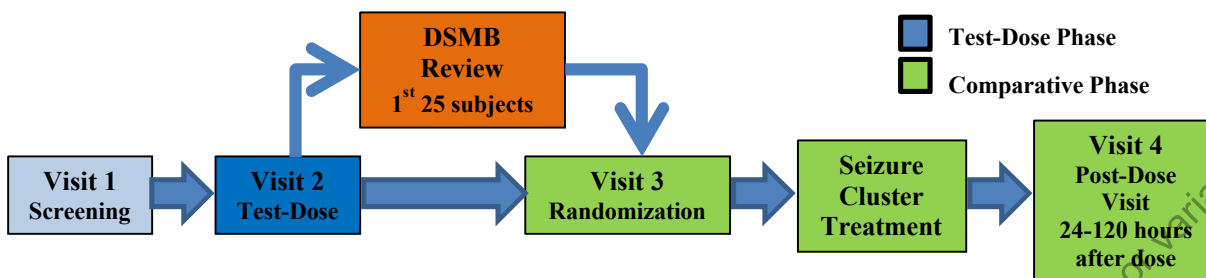
The Test-Dose Phase will be followed by the Comparative Phase, an outpatient, double-blind, placebo-controlled, parallel-group phase. In the Comparative Phase, all subjects will be randomized 2:1 to receive 5.0 mg USL261 or placebo. During the Comparative Phase, the subject's caregiver will administer the double-blind study drug when the subject experiences a seizure cluster that meets the study criteria, as described in the subject's individualized Patient Management Plan (PMP). If the treated seizure cluster 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 < 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 double-blind dose of study medication may be followed by a single dose of 5.0 mg USL261. Any time between 24 to 120 hours after study drug administration, subjects and caregivers will return to the study center for a post-dose study visit (Visit 4).

After Visit 3, the study coordinator or designee will call the caregiver or subject at least once each month until the subject has completed Visit 4 or has prematurely discontinued from the study.

After Visit 4, the subject will have completed the study and will be considered for enrollment in an open-label extension study, if one is offered at that time.

A maximum of approximately 350 subjects, aged 12 years or older, with a documented history of seizure clusters and on a stable AED regimen (no change in type[s] of drug) will be enrolled in the Test-Dose Phase. Before any subject continues to the Comparative Phase, safety data from at least 25 subjects in the Test-Dose Phase will be reviewed by an independent Data and Safety Monitoring Board (DSMB). Enrollment will temporarily halt once approximately 25 subjects complete the Test-Dose Phase, to allow the DSMB to review the safety data. If the safety data from this initial cohort supports continuation of the trial according to the DSMB, enrollment into the Test-Dose Phase will resume and the initial 25 subjects will proceed to the Comparative Phase. All subsequent subjects will progress directly from Test-Dose Phase to the Comparative Phase.

**Figure 1. Study Design**



### 3.2 Screening

After subjects and caregivers have provided informed consent (and assent, where appropriate), subjects will undergo screening procedures at Visit 1 (see [Table 1](#), Procedure Schedule). At Visit 1, training will be provided to the caregivers for self-study, which will be completed at or before Visit 2 (see [Section 9.3.3](#)). The screening period (time between Visit 1 and 2) will be a maximum of 28 days. The screening period may be extended in certain cases; however, the extension of the screening period must be approved by the Sponsor or CRO designee. If a screening period extension is granted for a given subject, that subject will have to undergo repeat screening laboratory and ECG assessments within 28 days before Visit 2.

### 3.3 Test-Dose Phase

The Test-Dose Phase, which occurs at Visit 2, will take place at the study center under the supervision of the study investigator within 28 days of Visit 1. The investigator, or other qualified study personnel, will review, assess, and (if needed) re-instruct subjects and caregivers on the information provided in the self-study training (see [Section 9.3.3](#)). Caregivers must pass the CPR exam and demonstrate airway management techniques before subjects are given a test dose.

Subjects who meet eligibility criteria at Visit 2 will receive a test dose of 5.0 mg USL261 administered by a member of the study center personnel followed by a second dose of 5.0 mg USL261 10 minutes later administered by the caregiver under the supervision of study center personnel. Caregivers and study center personnel will monitor the subject during the observation period for at least 4 hours after the test doses are administered and the

assessments outlined in [Table 1](#) will be performed. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, caregivers and study center personnel will monitor the subject during the observation period for at least 1 hour after test dose administration. A subject who experiences signs or symptoms at Visit 2 that are concerning in the investigator's judgment or are exclusionary per exclusion criterion #22 must be monitored until resolved or longer as deemed appropriate by the investigator.

At least one person who is trained and qualified to perform airway assessment and management, including endotracheal intubation (or local country/site equivalent) and Advanced Cardiac Life Support (ACLS) (or local country/site equivalent), will be available at the site for the entire observation period following the administration of the first test dose.

### **3.4 Comparative Phase**

Subjects and caregivers will return to the study center for Visit 3 within 24 hours to 28 days of Visit 2 (unless DSMB review is not yet completed). The time between Visit 2 and Visit 3 may be extended in certain cases; however, the extension must be approved by the Sponsor or CRO designee. At Visit 3, the investigator, or other qualified study personnel, will review, assess, and (if needed) re-instruct caregivers on the information provided in the self-study training. Before subjects are randomized, caregivers must have demonstrated hands-on competence in administering the study drug, performing timed respiration rate measurements and recording them in the practice Subject Worksheet, as well as demonstrate airway management techniques (see [Section 9.3.3](#)).

If the subject continues to meet eligibility criteria at Visit 3, he/she will be randomized to receive either USL261 5-mg or placebo. Caregivers will receive a study materials kit, which includes the Subject Workbook, the subject's PMP, and the study drug kit. The PMP will specify the criteria for seizure cluster recognition, the procedure for contacting the central study nurse hotline after study drug administration, the requirements for administering a second dose of study drug (USL261), and a rescue protocol individualized for the subject.

During the Comparative Phase, caregivers will administer the double-blind study medication at the time of recognition of a seizure cluster that meets study criteria (according to the subject's individualized PMP) and call the central study nurse hotline as soon as possible following study drug administration. If the treated seizure cluster 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  $< 8$  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 second dose of study drug (i.e., 5.0 mg dose of USL261) may be administered. If the second dose of study drug (i.e., 5.0 mg dose of USL261) is administered, the caregiver will again call the central study nurse hotline as soon as possible after its administration. The caregiver will monitor the subject after study drug administration to record safety and efficacy measurements (see [Section 6.1.4](#)).

If the subject encounters persistent seizure cluster activity or seizure recurrence (as defined in the subject's PMP), has less than 8 breaths per minute, or is excessively and uncharacteristically sedated, caregivers will follow the rescue protocol in the subject's PMP. The subject's rescue protocol will outline rescue instructions individualized for the subject, including when and how to contact EMS (or local equivalent).

Subjects and caregivers will return to the study center 24 to 120 hours after study drug administration for Visit 4. Subjects who are prematurely discontinued from study participation or terminate their participation should return to the study center for Visit 4 (Early Termination). The subject or caregiver will 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 (Visit 4 [Post-Dose Assessment or ET]) or 7 days after last administration of study drug, whichever is later. The subject or caregiver may also call the central study nurse hotline at any time during the study for help or advice regarding study procedures.

This study will be conducted in accordance with International Conference on Harmonization (ICH) E6, Guidelines 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 and 56 concerning informed consent and Institutional Review Board [IRB] regulations, respectively).

## **4 RATIONALE**

### **4.1 Rationale for the Study**

Although a substantial number of AEDs are currently marketed, a significant unmet need still exists in the treatment of epilepsy. Current AED therapies do not adequately control seizures (ie, seizure-freedom) in as many as 30% of epilepsy patients.[37, 38] Breakthrough seizures can occur in subjects with previously controlled epilepsy and may result from problems with treatment compliance (e.g., forgetting to take medication) or waning efficacy of current regimen. This study seeks to evaluate the treatment success rate and safety of USL261 compared with IN placebo for the outpatient treatment of seizure clusters in subjects with partial or generalized epilepsy with a documented history of seizure clusters on a stable regimen of antiepilepsy treatment(s).

### **4.2 Rationale for the Study Design**

The Test-Dose Phase was included to assess the safety, tolerability, and PK of USL261 in a monitored setting before subjects receive it as an outpatient during a seizure cluster. It will also allow study center personnel to effectively train the caregivers on study procedures, including study drug administration.

The Comparative Phase, consisting of a double-blind dose followed by a second dose of study drug (i.e., 5.0 mg dose of USL261), which is administered only if the subject experiences treatment failure, was designed to study the efficacy of 5.0 mg USL261 versus placebo, while allowing for the possibility that some subjects may require a higher dose to terminate the seizure cluster. Since caregivers and subjects will be aware that the second dose is active, there may be a “progression bias” prompting some to declare treatment

failure and administer the second dose. To reduce this possibility, and to increase the safety exposure in this study, subjects will be randomized 2:1, USL261:placebo.

The duration of each subject's participation will be determined by the frequency of observed seizure events. Assuming an average of 3 seizure clusters per year, approximately half of the study subjects will complete the study within ~4 months after randomization to treatment. Subjects may remain in the Comparative Phase for up to 6 months. Any subject who has not treated a seizure cluster meeting the study criteria within 6 months of Visit 3 (Randomization) will be discontinued from the study.

### 4.3 Rationale for Dosing Regimen

The 5.0 mg dose of USL261 used for this phase III trial is based on safety data reported in 2 ITI-sponsored 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 min 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, the 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 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 patients diagnosed with epilepsy (MZ0815) who were taking concomitant medications, including AEDs known to induce CYP450 3A4. 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 demonstrate that 0.1 to 0.3 mg/kg of IV-approved midazolam administered intranasally (5 mg to > 20 mg fixed-dose per subject) effectively terminates seizure activity in most subjects.[21, 25, 39] These doses have seldom caused excessive sedation or respiratory depression.[40]

The 5.0 mg midazolam dose proposed for the Comparative Phase of this study is expected to be safe and efficacious. The 10 mg dose of midazolam provided by USL261 is well within the range of doses correlated with efficacy and has been found to be safe. [18, 31]

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 by 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 Required

A maximum of approximately 350 subjects are expected to be enrolled in the Test Dose Phase of the study in order to have a maximum of approximately 240 subjects who have completed the Comparative Phase.

### 5.2 Inclusion Criteria

A subject will be eligible for enrollment in the study if all of the following criteria apply:

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 IRB/Independent ethics committee (IEC) policy
2. Subject has a competent, adult (age  $\geq 18$ ) caregiver(s) who is able to recognize and observe the subject's seizure cluster episodes, 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 is not likely to conceive, as indicated by a "yes" answer to at least 1 of the following questions:
  - Is the subject is a male?
  - Is the subject a postmenopausal female with greater than 1 year since last menses and a follicular stimulating hormone value greater than 40 mIU/mL?
  - Is the subject a female who has written medical documentation of being permanently sterilized (e.g., hysterectomy, double oophorectomy, bilateral salpingectomy)?
  - Has the subject agreed to use two effective methods of contraception during the entire study if she is sexually active or becomes 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. Subject has an established diagnosis of partial or generalized epilepsy that includes **all** of the following:

- A documented history of seizure clusters lasting a minimum of 10 minutes from the time the seizure cluster is recognized
- The 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
- 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
- In the investigator's opinion, it would be safe for the subject to receive placebo as a first dose of study drug followed by active treatment (USL261) as the second dose of study drug no earlier than 10 minutes after the first dose
- The subject's stereotyped seizure cluster pattern is composed of multiple ( $\geq 2$ ) partial or generalized seizures
- The subject's stereotyped seizure cluster pattern was established  $> 3$  months before Visit 1
- A frequency of  $\geq 3$  stereotyped seizure clusters during the year before Visit 1
- At least 1 stereotyped seizure cluster occurring  $\leq 4$  months before Visit 1

- The seizure cluster pattern described above is confirmed by a central reviewer (see [Section 9.3.1](#))
6. Subject is receiving a regimen of AED(s) that has been stable (i.e., no changes in the type of AED) since Visit 1 and for  $\geq 7$  days before Visit 2. Changes in dose of an AED are allowed during the study; however, the new dose level must be kept stable for at least 7 days before the subject receives study drug. Benzodiazepines that are used for rescue therapy of seizures or for non-epilepsy indications are allowed provided they are typically used  $\leq 3$  days in a 7-day period on average and always at the same dose. Daily use of a benzodiazepine as a chronic AED is not permitted.
  7. Subject has had a documented brain computerized tomography or magnetic resonance imaging review, performed after diagnosis of epilepsy and before Visit 1, that confirms the absence of a progressive neurological disorder
  8. Subject weight is 40 kg to 125 kg (inclusive)
  9. Subject must have a screening (Visit 1) 12-lead electrocardiogram (ECG) that meets the following criteria:
    - QTcF interval  $\leq 450$  msec for males and  $\leq 470$  msec for females
    - Consistent sinus rhythm as determined by the investigator
    - No left bundle branch block (LBBB)
    - No other clinically significant conduction disorders as determined by the investigator
  10. Subject must have screening (Visit 1) vital sign values that meet the following criteria:
    - Systolic blood pressure of  $\leq 160$  mm Hg
    - Diastolic blood pressure of  $\leq 90$  mm Hg
    - Pulse rate of 50 to 115 bpm, inclusive
    - No clinically significant vital sign values as determined by the investigator

Note: At the discretion of the investigator, out-of-range BP or HR measurements may be repeated once, and the repeat measurement used in relation to this inclusion criterion.

### 5.3 Exclusion Criteria

A subject will not be eligible for this study if any of the following criteria apply:

#### At Visit 1 (Screening)

1. Subject has a neurological disorder that is likely to progress in the next year
2. Subject has acute narrow-angle glaucoma
3. 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
4. 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
5. Subject has had psychogenic, non-epileptic seizure(s) within the 5 years before Visit 1
6. Subject has suicidality, defined as any of the following: a) active suicidal plan/intent or active suicidal thoughts in the 6 months before Visit 1 as defined by a Columbia-Suicide Severity Rating Scale (C-SSRS) suicidal ideation score  $\geq 3$ , b) any suicide attempt in the past 5 years as determined by the C-SSRS or medical history, or c) other clinically significant suicidality as determined by the investigator
7. Subject, in the investigator's opinion, has met the criteria for a major depressive episode at any time within 6 months before Visit 1 (criteria defined by the current edition of the *Diagnostic and Statistical Manual of Mental Disorders*)
8. Subject has or has had psychosis in the 12 months before Visit 1, excluding postictal psychosis
9. Subject has a history of their stereotypical seizure cluster (for which they are being enrolled in the study) progressing to status epilepticus (as determined by the investigator) within the 2 years before Visit 1
10. Subject has a history of drug or alcohol abuse within 1 year before Visit 1
11. Subject has a positive pregnancy test at Visit 1 or is currently pregnant or breastfeeding (females only)

12. Subject has a history of allergy or any significant adverse reaction (including rash) to midazolam
13. Subject is currently using an investigational drug or device or has used such within 30 days before Visit 1
14. Subject is currently using a vagal nerve stimulator (VNS) unless the device has been implanted for at least 6 months and the settings have not changed within 4 weeks before Visit 1
15. Subject has plasma phenobarbital concentrations  $> 35 \mu\text{g/mL}$  at Visit 1 (phenobarbital concentrations will be measured in subjects taking phenobarbital and in subjects for which the investigator deems it necessary)
16. Subject has any clinically significant laboratory abnormality as determined by the investigator and as confirmed by repeat testing (see [Section 6.2.2.7.2](#)), or has any of the following laboratory abnormalities at Visit 1 as confirmed by repeat testing:
  - Alanine transaminase (ALT) and/or aspartate transaminase (AST) results  $> 2$  times the upper limit of normal
  - White blood cell count (WBC)  $< 2.5 \times 10^9/\text{L}$
  - Sodium  $< 128 \text{ mEq/L}$
  - Creatinine  $> 2.0 \text{ mg/dL}$
17. Subject is not appropriate for the study for any other reason as determined by the investigator

At Visit 2

18. Subject has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory abnormality, or required a new treatment or medication which meets any previously described study exclusion criteria
19. Subject has a positive pregnancy test (females only)
20. Subject has active suicidal plan/intent or suicidal thoughts as defined by a C-SSRS suicidal ideation score  $\geq 3$  or has had a suicide attempt since the last visit

21. Subject has consumed any clinically significant CYP450 3A inhibitor/inducer, opioid, or other respiratory depressant (excluding antiepileptic drugs) within the required washout period before Visit 2 (see [Appendix 1](#))
22. Subject has any of the following during the observation period after administration of the USL261 test dose at Visit 2:
- Blood pressure (BP)
    - Systolic blood pressure (SBP) < 85 mm Hg and the change from baseline (pre-dose evaluation) in SBP is deemed clinically significant by the investigator
    - A  $\geq 40$  mm Hg decrease from baseline (pre-dose evaluation) in SBP
    - Diastolic blood pressure (DBP) < 50 mm Hg and the change from baseline (pre-dose evaluation) in DBP is deemed clinically significant by the investigator
    - A  $\geq 30$  mm Hg decrease from baseline (pre-dose evaluation) in DBP
  - Heart Rate (HR)
    - HR > 120 or < 50 bpm and change from baseline (pre-dose evaluation) in HR is deemed clinically significant by the investigator
    - A  $\geq 40$  bpm change from baseline (pre-dose evaluation) in HR
  - Respiratory rate (RR)
    - RR > 24 breaths per minute and change from baseline (pre-dose evaluation) in RR is deemed clinically significant by the investigator
    - RR < 8 breaths per minute while awake or after arousing
  - Sedation to the degree that the subject does not respond to mild prodding or shaking
  - Oxygen saturation < 90% for > 30 seconds or requires oxygen at any time
  - Clinically-significant ECG findings as determined by the investigator
- Note: At the discretion of the investigator, out-of-range BP or HR measurements may be repeated once, and the repeat measurement used in relation to exclusion criteria, as long as the rules outlined in [Section 6.2.2.3](#) are followed.

### At Visit 3

23. Subject has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory abnormality, or required a new treatment or medication which meets any previously described study exclusion criteria
24. Subject has a positive pregnancy test
25. Subject has active suicidal plan/intent or suicidal thoughts as defined by a C-SSRS suicidal ideation score  $\geq 3$  or has had a suicide attempt since the last visit

## 5.4 Informed Consent

Each prospective subject or the subject's LAR will provide written informed consent before any 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.

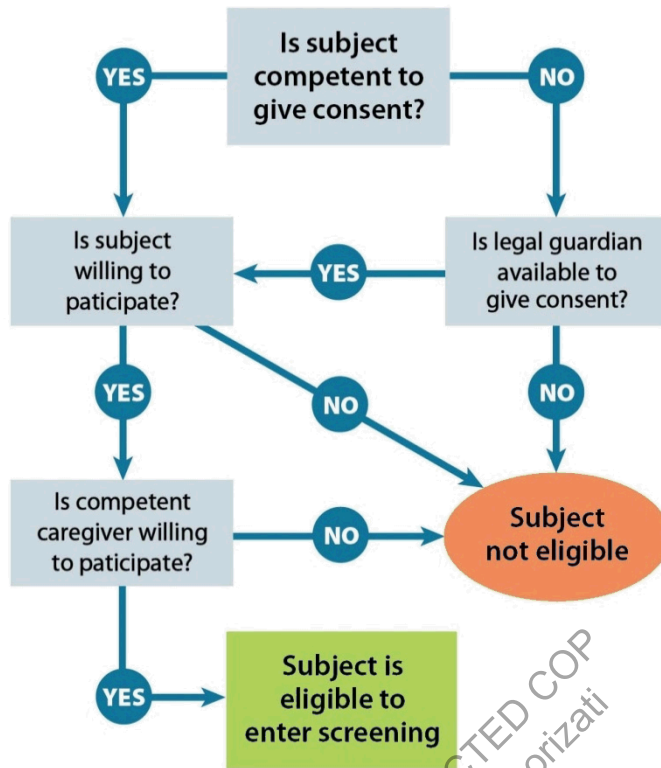
Some subjects will provide written consent in the form of an assent form before any screening evaluation or other study procedure is performed, if required by local law or IRB/EC policy. In these cases, the ICF will be signed by the subject's LAR. The assent form will provide similar information as the informed consent form, and the same procedures will be followed as described above for the informed consent form. 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 informed consent form with the study protocol for IRB/IEC approval. All proposed informed consent forms 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 only applies to study centers in the United States.

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 legally acceptable representative 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 LAR will voluntarily sign and date an authorization document. Prior to participation in the study, the subject or 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 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.

#### **6.1.1 Visit 1 (Screening Visit)**

Before any study procedure is performed, the subject (or subject's LAR) will provide written informed consent (see [Section 5.4](#)). At Visit 1, subjects will undergo screening

assessments to determine if they are eligible to participate in the study according to the inclusion/exclusion criteria. The following evaluations will be performed during Visit 1:

At Visit 1 (Screening)

- Obtain informed consent of subject (or subject's LAR) (see [Section 5.4](#))
- Obtain assent of subject, if applicable (see [Section 5.4](#))
- Obtain informed consent of caregiver(s) (see [Section 5.4](#))
- Register subject with Interactive Response Technology System (IRT)
- Assessment of inclusion/exclusion criteria (see [Section 5](#))
- Provide training to caregiver for self-study (see [Section 9.3.3](#))
- Collect demographic information (e.g., date of birth, gender, ethnic origin, race)
- Collect medical and surgical history, including current disease (see [Section 6.2.2.1](#))
- Collect prior and concomitant medication information (see [Section 6.3](#))
- Collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency in the year prior to screening.
- Complete physical, nasal, and neurological examinations (see [Section 6.2.2.2](#))
- Collect blood and urine samples for clinical laboratory testing (serum chemistry, hematology, urinalysis and phenobarbital level [if necessary]) and FSH level (females only); (see [Section 6.2.2.7](#))
- Collect blood sample for serum pregnancy test (all females) (see [Section 6.2.2.7](#))
- Collect urine sample for urine drug screen and blood sample for alcohol test (see [Section 6.2.2.7](#))
- Begin preparation of PMP (see [Section 9.3.1](#))
- Submit PMP, including seizure cluster descriptions, to Central Reviewer (see [Section 9.3.1](#))
- Perform 12-lead ECG (see [Section 6.2.2.4](#))
- Measure height and weight
- Measure vital signs (BP, HR, RR, and temperature) (see [Section 6.2.2.3](#))
- Perform the Baseline/Screening C-SSRS (see [Section 6.2.2.8](#))
- Collect any adverse events occurring after written informed consent is obtained

## 6.1.2 Visit 2 (Test-Dose)

Once initial eligibility is confirmed but no later than 28 days from Visit 1, subjects and caregivers will enter the Test-Dose Phase to assess the safety, tolerability, and PK of USL261 and provide the caregivers training on study procedures, including study drug administration. All caregivers must be present at Visit 2 for this training, except for new caregivers who are assigned after Visit 2. At least 1 person who is trained and qualified to perform airway assessment and management, including endotracheal intubation (or local country/site equivalent) and ACLS (or local country/site equivalent), must be available at the site for the entire observation period. Prior to 132 subjects completing the Comparative Phase the observation period will be at least 4 hours following test dose administration. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, the observation period will be defined as at least 1 hour following test dose administration.

### 6.1.2.1 Before Administration of Test Dose at Visit 2

The investigator or other qualified study center personnel will perform the following before administration of the USL261 test dose at Visit 2:

- Review of inclusion/exclusion criteria (see [Section 5](#))
- Caregiver training (see [Section 9.3.3](#))
  - Review, assess, and re-instruct (when needed) caregivers on the information provided in the self-study training
  - Ensure caregiver has passed the CPR exam and can demonstrate the correct technique for airway management (including neck extension, chin lift, and jaw thrust maneuvers)
- Collect concomitant medication information (see [Section 6.3](#))
- Complete physical, nasal and brief neurological examinations (see [Section 6.2.2.2](#))
- Administer B-SIT (see [Section 6.2.2.9](#))
- Perform a urine pregnancy test (all females) (see [Section 6.2.2.7](#))

- Ensure that the PMP is finalized before a subject receives a test dose of USL261 (see [Section 9.3.1](#))
- Collect blood sample for PK analysis (see [Section 6.2.3](#))
- Perform baseline OAA/S (see [Section 6.2.2.5](#))
- Perform baseline 12-lead ECG (see [Section 6.2.2.4](#))
- Measure body weight
- Measure baseline vital signs (BP, HR, respiration rate, temperature) (see [Section 6.2.2.3](#))
- Measure baseline oxygen saturation with pulse oximetry (see [Section 6.2.2.6](#))
- Perform C-SSRS (see [Section 6.2.2.8](#))
- Administer the subject outcome assessments (see [Section 6.2.5](#))

Caregivers will perform the following assessments before administration of the USL261 test dose at Visit 2:

- Demonstrate the correct technique for airway management (including neck extension, chin lift, and jaw thrust maneuvers)
- Monitor and record the baseline respiration rate of the subject (see [Section 6.2.2.3](#))
- Complete the caregiver outcome assessments (see [Section 6.2.5](#))

#### **6.1.2.2 Administration of Test Dose at Visit 2**

Subjects who continue to meet all eligibility criteria will receive 2 doses of 5.0 mg USL261 10 minutes apart.

- Study center personnel will administer the first dose
- Subject's primary caregiver will administer the second dose under supervision of qualified study personnel

#### **6.1.2.3 Post-Administration of Test Dose at Visit 2**

Study personnel and the caregiver will monitor the subject for the entire observation period. Prior to 132 subjects completing the Comparative Phase, the observation period will be 4

hours. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, the observation period will be at least 1 hour following test dose administration. Assessments occurring at the same time should be completed in the following order: ECG, OAA/S, measurement of vital signs (including respiration rate), pulse oximetry, blood draw for PK analysis and second test dose.

Study center personnel will perform the following:

- Perform 12-lead ECG approximately 15 minutes after the first test dose (see [Section 6.2.2.4](#))
- Perform OAA/S at approximately 5, 10, 20, 30 minutes and 1, 2 and 4 hours after the first test dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, perform OAA/S at approximately 5, 10, 20, 30 minutes and 1 hour after the first test dose (see [Section 6.2.2.5](#))
- Record vital signs (BP, HR, and respiration rate at approximately 5, 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 3, and 4 hours after administration of the first dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, record vital signs (BP, HR, and respiration rate at approximately 5, 10, 15, 20, 30, 45 minutes and 1 hour after administration of the first dose (see [Section 6.2.2.3](#))
- Record pulse oximetry at approximately 5, 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 3, and 4 hours after administration of the first dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, record pulse oximetry at approximately 5, 10, 15, 20, 30, 45 minutes and 1 hour after administration of the first dose (see [Section 6.2.2.6](#))
- Collect blood samples for PK analysis at approximately 5, 10, 20, 30 minutes, and 1, 2, and 4 hours after administration of the first dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, collect blood samples for PK analysis at approximately 5, 10, 20, 30 minutes, and 1 hour after administration of the first dose (see [Section 6.2.3](#))
- Collect and record AEs

- Call the Interactive Response Technology System (IRT) to report test-dose information

Caregivers will perform the following and record the assessments into a practice Subject Worksheet:

- Under the supervision of study center personnel, the caregiver will monitor and record respiration rate of the subject at approximately 5, 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 3, and 4 hours after the first test dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, the caregiver will monitor and record respiration rate of the subject at approximately 5, 10, 15, 20, 30, 45 minutes and 1 hour after the first test dose. To determine respiration rate, the caregiver will count the number of breaths taken by the subject during a 30-second interval (see [Section 6.2.2.3](#)).

A subject who experiences signs or symptoms at Visit 2 that are concerning in the investigator's judgment or are exclusionary per exclusion criterion #22 must be monitored until resolved or longer as deemed appropriate by the investigator. Subjects who no longer meet eligibility criteria after the Test-Dose Phase (see [Section 5.3](#), Exclusion Criteria) and/or have decided not to participate further in the trial will proceed to the Early Termination (ET) visit and complete the Visit 4 procedures (see [Section 6.1.6](#)).

### **6.1.3 DSMB Assessment (After 25 Subjects Complete Visit 2)**

Before any subject is enrolled in the Comparative Phase, safety data from at least 25 subjects in the Test-Dose Phase will be reviewed by the DSMB. Enrollment will temporarily halt once approximately 25 subjects complete the test dose visit, to allow the DSMB to review the safety data. If the DSMB findings indicate that administering 2 doses of USL261 5.0 mg (total 10 mg) meets safety requirements, the study will continue as planned. Subjects from the Test-Dose Phase whose data were analyzed by the DSMB will be randomized at Visit 3, and all subsequent subjects will proceed from Visit 2 to Visit 3 as outlined below.



### 6.1.4 Visit 3 (Randomization)

For subjects enrolled in the study after the initial DSMB review, Visit 3 will take place between 24 hours and 28 days after Visit 2. The time between Visit 2 and Visit 3 may be extended in certain cases; however, the extension must be approved by the Sponsor or CRO designee. At Visit 3, the subject will be randomized to receive either USL261 or placebo, if he or she continues to meet the eligibility criteria (Section 5). At Visit 3, the investigator or other qualified study personnel will perform the following:

- Review of inclusion/exclusion criteria (see Section 5)
- Caregiver training
  - Review, assess, and re-instruct (when needed) caregivers on the information provided in the self-study training
- Ensure caregiver has demonstrated hands-on competence in administering the study drug, measuring timed respiration rate, recording information in a practice Subject Worksheet and performing the correct technique for airway management (including neck extension, chin lift, and jaw thrust maneuvers)
- Collect concomitant medication information
- Complete physical, nasal and brief neurological examinations (see Section 6.2.2.2)
- Administer B-SIT (see Section 6.2.2.9)
- Perform a urine pregnancy test (all females)
- Review the PMP with the subject and caregiver
- Measure body weight
- Measure vital signs (BP, HR, respiration rate, temperature) (see Section 6.2.2.3)
- Perform C-SSRS, Since Last Visit version (see Section 6.2.2.8)
- Call the Interactive Response Technology System (IRT) to obtain the study drug kit identification number to be dispensed
- Provide subjects/caregivers with study kit, which includes at a minimum:
  - Individualized PMP
  - Individualized Summary of the PMP (i.e., laminated card for convenient reference)

- Subject Workbook
- Study drug kit
- Dosing instructions
- Collect and record AEs

The investigator or his/her designee will confirm that the subject and caregiver clearly understand the study procedures (e.g., requirements for documenting seizure activity, timing for respiration rate monitoring, etc.) before leaving the study center. Caregivers will again be reminded to call the central study nurse hotline as soon as study drug is administered. If caregivers give the second dose, a call to the central study nurse is required as well.

### 6.1.5 Treatment

The caregiver will document in the Subject Workbook all seizure activity that occurs from the time the subject and caregiver receive the study materials kit at Visit 3 until Visit 4 or Early Termination (ET). Seizure activity 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 and untreated seizures should also be recorded, with the information estimated to the best of the subject's or caregiver's ability.

When a seizure cluster that meets study criteria (per the subject's individualized PMP) is identified, the caregiver will:

- Note the time of recognition of the seizure cluster onset
- Administer the double-blind study drug intranasally
- Note the time of study drug administration
- Call the central study nurse hotline as soon as possible after administering the study drug; a central study nurse will assist the caregiver in making study-related efficacy and safety assessments, if needed, and will be responsible for safety monitoring following administration of study drug

- Measure and record subject's respiration rate by counting the number of breaths taken in a 30-second interval at approximately 15 and 30 minutes, and 1, 2, and 4 hours after study drug administration (respiration rate will be measured at these times whether or not the seizure cluster has ended, unless, for reasons of subject safety, it cannot be performed)
- Ensure the rescue protocol in the PMP is followed if the subject has less than 8 breaths per minute, is excessively and uncharacteristically sedated or other criteria outlined in the rescue protocol are met
- Administer the second dose of study drug (i.e., 5.0 mg dose of USL261) if (see [Section 6.1.7.2.2](#)):
  - 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
  - There is no evidence of excessive, uncharacteristic marked sedation (as defined by the investigator in the PMP), the subject does not have a respiratory rate less than 8 breaths per minute, and the subject does not require emergency rescue treatment with assisted breathing or intubation

If the second dose of study drug (i.e., 5.0 mg dose of USL261) is administered, the caregiver will do the following:

- Call the central study nurse hotline as soon as possible after the second dose is administered
- Ensure the rescue protocol in the PMP is followed if the subject has less than 8 breaths per minute, is excessively and uncharacteristically sedated, or seizure cluster activity persists or recurs following the administration of the second dose; the subject's rescue protocol will outline what is considered to be persistent or recurrent seizure activity and uncharacteristic sedation for the particular subject

After the seizure cluster has ended, the caregiver will do the following:

- Evaluate 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 following information is recorded in the Subject Workbook
  - Date and start time when the treated seizure cluster was recognized
  - All seizure activity
  - Date and time of study drug administration(s)
  - Respiration rate measurements and the date(s) and times they were collected (see [Section 6.2.2.3](#))
  - Any changes in the subject's overall health for 24 hours after receiving study drug
  - Medications that the subject received and device use by the subject in the 24 hours following study drug administration
- Continue to record all seizure activity until Visit 4 in the Subject Workbook
- Re-package the study drug (used and unused) for return

Upon receiving a call from the caregiver stating the study drug (first, double-blind dose and/or second dose [ie, 5.0 mg dose of USL261]) had been administered, a central study nurse may do the following:

- Assist the caregiver in completing study assessments accurately and on time according to the protocol, if needed; a central study nurse will have access to all individualized PMPs so they are aware of each subject's seizure morphology
- Help the caregiver to determine if the rescue protocol in the PMP needs to be activated, if necessary
- Notify the investigator within 24 hours that the subject received drug and will need to schedule follow-up visit; site personnel will then contact both caregiver and subject to schedule Visit 4

### 6.1.6 Visit 4 (Post-Dose Assessment or Early Termination)

Subjects and caregivers will return to the study center for Visit 4 between 24 and 120 hours (i.e., 1 to 5 days) after study drug administration. Subjects who are prematurely discontinued from study participation or terminate their participation should return to the study center for Visit 4 (Early Termination). Any subject who has not treated a seizure cluster meeting the study criteria within 6 months of Visit 3 (Randomization) will be discontinued from the study and will return to the study center for Visit 4 (Early Termination).

At Visit 4 (Post-Dose or Early Termination [ET]), the investigator or other qualified study personnel will do the following:

- Collect concomitant medication information
- Collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since Visit 3 or the most recent follow-up phone call.
- Complete physical, nasal and neurological examinations (see [Section 6.2.2.2](#))
- Collect blood and urine samples for clinical laboratory testing (serum chemistry, hematology, and urinalysis) (see [Section 6.2.2.7](#))
- Perform urine pregnancy test (all females)
- Measure body weight and height
- Measure vital signs (BP, HR, respiration rate, temperature) (see [Section 6.2.2.3](#))
- Administer B-SIT (see [Section 6.2.2.9](#))
- Perform C-SSRS, Since Last Visit version (see [Section 6.2.2.8](#))
- Administer the subject and caregiver outcome assessments (see [Section 6.2.5](#)) Collect and record AEs
- Collect study drug and container(s) (used and unused)
- Review and collect the Subject Workbook

## **6.1.6.1 Telephone Follow-Up and Support**

### ***6.1.6.1.1 Telephone Follow-up***

After Visit 3, the study coordinator or designee will call the caregiver or subject at least once each month until the subject has completed Visit 4 or has prematurely discontinued from the study. On these telephone calls, a member of the study center personnel will do the following:

- Verify that at least 1 trained caregiver is still available
- Ask about any seizure clusters that occurred
- Ask about whether the study materials kit is still accessible and available
- Review study procedures
- 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 Visit 3 or the most recent follow-up phone call.

### ***6.1.6.1.2 Central study nurse hotline***

A toll-free hotline with access to a central study nurse(s) will be available 24 hours a day, 7 days a week to assist subjects and caregivers who need additional information on study procedures or general advice and support. It is a requirement for caregivers to call the central study nurse hotline as soon as possible after administering study treatment, including the second dose if needed, for the subject's seizure cluster episode. A central study nurse will assist the caregiver in making study-related efficacy and safety measurements, if needed, and will be responsible for safety monitoring following the administration of study drug. A central study nurse(s) will have access to all subject's individualized PMPs so they are aware of each subject's seizure morphology and can help the caregiver determine if the rescue protocol needs to be activated.

A member of the study center staff will be notified by either a central study nurse or the CRO [inVentiv Health Clinical] that a subject has received study drug. The study coordinator at the study center (or designee) will contact the caregiver and/or subject to schedule Visit 4, which will occur in the 24 to 120 hours after study drug administration.

## **6.1.7 Dosing Instructions**

### **6.1.7.1 Test-Dose Phase Dosing**

The test dose administered at Visit 2 is an open-label dose of USL261 administered in 2 parts: a single 5.0 mg dose (1 actuation) into either nostril, followed 10 minutes later by a second 5.0 mg dose (1 actuation), administered in the opposite nostril.

The first dose will be administered by study personnel and the second dose by the primary caregiver under the supervision of qualified study personnel.

### **6.1.7.2 Comparative Phase Dosing**

#### ***6.1.7.2.1 Dosing Double-Blind Study Medication***

During the Comparative Phase, the caregiver will administer to the subject 1 actuation of the double-blind study drug, to which they have been randomized (5.0 mg USL261 or a matching placebo nasal spray), into either nostril upon occurrence of a qualifying seizure cluster.

#### ***6.1.7.2.2 Dosing of Second Dose (i.e., 5.0 mg dose of USL261)***

The caregiver may administer a second dose of study drug (i.e., 5.0 mg dose of USL261) into the subject's opposite nostril if the following criteria are met:

- The initial seizure cluster has not terminated within 10 minutes after the initial drug administration, provided that the subject does not have < 8 breaths per minute, does not require emergency rescue treatment with assisted breathing or intubation and does not have or excessive, uncharacteristic, marked sedation (as defined by the investigator in the PMP),

OR

- Another seizure occurs between 10 minutes and 6 hours after administration of the double-blind study drug, provided that the subject does not have < 8 breaths per minute, does not require requiring emergency rescue treatment with assisted breathing or intubation and does not have excessive, uncharacteristic, marked 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](#)).

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
- Date, start, and stop time of each seizure within 24 hours after any study drug administration
- 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**

A complete medical history will be collected by qualified medical personnel participating in the study for each subject, including seizure history. Medical history will be taken and recorded at Visit 1. Changes to medical history will be reviewed by the Investigator and noted if appropriate as an AE.



### **6.2.2.2 Physical and Neurological Examinations**

Physical 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, and a nasal cavity examination using a nasal speculum. During the nasal exam, special attention will be paid to signs of nasal congestion and signs of abrasion or trauma. Complete physical examinations will be conducted at Visits 1, 2, 3, and 4 / ET. Height will be measured at Visits 1 and 4/ET.

Complete neurological examinations will be conducted at Visits 1 and 4 / ET. The complete neurological exam will consist of evaluations of the following: Mental status (including orientation, memory and quality/fluency of speech), cranial nerves II-XII, motor strength of the upper and lower limbs, deep tendon and plantar reflexes, sensory exam, station and gait, hopping, Romberg test, finger-to-nose test, heel-to-shin test, rapid alternating movements, nystagmus, and tremor or other abnormal movements. A partial neurological examination will be conducted at Visits 2 and 3 and will consist of evaluations of the following: Mental status (including orientation, memory and quality/fluency of speech), station and gait, finger-to-nose test, heel-to-shin test, rapid alternating movements, nystagmus, and tremor or other abnormal movements. Neurological examinations will be conducted by a qualified investigator or sub-investigator.

Any clinically-significant abnormality identified during the physical or neurological examination at Visit 1 will be recorded in the subject's medical history. 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.

Vital signs to be collected include the following:

- Systolic and diastolic BP
- HR
- Respiration rate
- Temperature

At Visits 1, 3, and 4 or ET, the vital signs listed above will be measured while subjects are seated and at rest for a minimum of 5 minutes.

At Visit 2, qualified study personnel will review and record in source documents the subject's BP, respiration rate, and HR before and at 5, 10, 15, 20, 30, 45, and 1, 1.5, 2, 3, and 4 hours after the administration of the first test dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, study personnel will review and record in source documents the subject's BP, respiration rate, and HR before and at 5, 10, 15, 20, 30, 45, and 1 hour after the administration of the first test dose. Temperature will be measured only at the pre-dose time point at Visit 2.

As part of their training, caregivers will measure the subject's respiration rate at these same time points and record the findings in a practice worksheet under the supervision of study personnel. To determine respiration rate, the caregiver will count the number of breaths taken by the subject during a 30-second interval.

During the Comparative Phase of the study, caregivers will measure respiration rate at approximately 15 and 30 minutes, and 1, 2, and 4 hours after study drug administration. 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.

At the discretion of the investigator, out-of-range BP or HR measurements may be repeated and the repeat measurement used in relation to inclusion / exclusion criteria, as long as the following are rules are followed:

- The repeat measurement must be made within 15 minutes after the out-of-range measurement

- The repeat measurement must be made before the next designated time point
- For each individual vital sign parameter (e.g. SBP), only one repeat measurement is allowed at each time point
- There cannot be more than three repeat measurements for an individual vital sign parameter (e.g. SBP) in total over the entire observation period at Visit 2

#### **6.2.2.4 Electrocardiogram (ECG)**

A 12-lead ECG will be performed at Visit 1. In order to be eligible for the study, a subject must have a screening (Visit 1) 12-lead ECG that meets the criteria outlined in [Section 5.2](#).

During Visit 2, a 12-lead ECG will be performed before and at 15 minutes after the first 5.0 mg test dose. Subjects with clinically significant ECG findings at Visit 2, as determined by the investigator, will be discontinued from the study.

ECGs will be centrally reviewed by a cardiologist and by the investigator or designee. An ECG report will be sent to the study center by the central ECG vendor; the investigator will review the ECG report and indicate the clinical significance of all abnormal findings, and then sign and file the ECG report in the subject's study file. ECG procedures will be provided to all study centers by the central ECG vendor study initiation.

#### **6.2.2.5 Observer's Assessment of Alertness/Sedation Scale (OAA/S)**

The OAA/S scale is a validated qualitative categorical measure of sedation.[41] The OAA/S scale is composed of the following assessment categories: responsiveness, speech, facial expression, and eyes.

The OAA/S scale will be scored in 2 ways; a composite score, defined as the lowest score in any one of the 4 assessment categories and a sum score, which is calculated as the total of the scores in the 4 assessment categories.

The OAA/S will be administered at Visit 2 before and at 5, 10, 20, 30 minutes and 1, 2, and 4 hours after the first test dose by a qualified member of the study center personnel. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, the

OAA/S will be administered at Visit 2 before and at 5, 10, 20, 30 minutes and 1 hour after the first test dose.

#### **6.2.2.6 Pulse Oximetry**

At Visit 2, O<sub>2</sub> saturation will be measured using pulse oximetry. Oxygen saturation will be recorded in the source document before and at 5, 10, 15, 20, 30, 45 minutes, and at 1, 1.5, 2, 3, and 4 hours after administration of the first 5.0 mg test dose. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, oxygen saturation will be recorded in the source document before and at 5, 10, 15, 20, 30, 45 minutes, and at 1 hour after administration of the first 5.0 mg test dose.

An observation of O<sub>2</sub> saturation < 90% will be recorded as an AE, if O<sub>2</sub> saturation remains below 90% for > 30 seconds. The pulse oximetry device placement and function will be confirmed by qualified study center personnel, and subjects will be clinically assessed to determine the validity of the recording.

#### **6.2.2.7 Clinical Laboratory Assessments**

All subjects will have the clinical laboratory tests performed as listed in [Table 4](#). The total volume of blood collected for clinical laboratory assessments will be approximately 20 mL (1.5 tablespoons) per subject. Subject fasting is not required before collection of clinical laboratory blood or urine samples.

All females will undergo a serum pregnancy test at Visit 1 and urine pregnancy tests for beta-human chorionic gonadotropin ( $\beta$ -hCG) at Visits 2, 3, and 4. Test results must be negative at these visits for a subject to be enrolled or continue in the 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. 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**

<b>Hematology (Visits 1 and 4 / ET)</b>	<b>Serum Chemistry (Visits 1 and 4 / ET)</b>
CBC with differential	A/G ratio
Hgb	Albumin
Hct	AP
MCV	ALT (SGPT)
MCH	AST (SGOT)
MCHC	Bicarbonate
Platelets	BUN
RBC	BUN/Creatinine ratio
WBC	Calcium
<b>Pregnancy Test[a] (Visits 1, 2, 3, 4/ET) (Females only)</b>	Cholesterol (total)
β-hCG	Cholesterol/HDL ratio
<b>Drug Screen (Visit 1 only)</b>	Cholesterol/LDL ratio
Amphetamines	Chloride
Barbiturates	Creatinine
Benzodiazepines	GGT
Cannabinoids	Globulin
Cocaine metabolites	Glucose
Ethyl alcohol[b]	HDL cholesterol
Opiates	Iron
Phencyclidine	LDH
<b>Plasma phenobarbital[c] (Visit 1 only)</b>	LDL cholesterol
<b>Urinalysis (Visits 1 and 4 / ET)</b>	Phosphorus
Bilirubin	Potassium
Blood	Sodium
Glucose	Total/direct bilirubin
Cells (WBC, RBC, epithelial)	Total protein
Ketones	Triglycerides
Leukocytes	Uric acid
Nitrites	<b>Additional Screening Test (Visit 1 only)</b>
pH	FSH (females only)
Protein	
Specific gravity	
Urobilinogen	

Abbreviations: β-hCG, beta-human chorionic gonadotropin; ALT (same as SGPT), alanine aminotransferase; AP, alkaline phosphatase; AST (same as SGOT), aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; GGT, gamma-glutamyl transpeptidase; Hct, hematocrit; HDL, high-density lipoprotein; Hgb, hemoglobin; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; pH, hydrogen ion concentration; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

[a] Serum β-hCG levels measured at Visit 1, urine β-hCG levels measured at Visits 2, 3, 4

[b] Blood alcohol screen

[c] Only for subjects taking phenobarbital and for subjects for which the investigator deems it necessary.

#### **6.2.2.7.1 Sample Collection, Storage, and Shipping**

Blood and urine specimens will be collected by qualified study center personnel and sent to and analyzed by a central laboratory for the hematology, urinalysis, serum chemistry, urine drug screen, and blood alcohol analyses. Laboratory test results will be flagged by the central laboratory if they meet protocol specified inclusion/exclusion criteria (e.g., WBC <  $2.5 \times 10^9/L$ ). 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.

#### **6.2.2.7.2 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.

#### **6.2.2.8 Columbia-Suicide Severity Rating Scale (C-SSRS)**

The C-SSRS is a clinician-rated scale that assesses suicidal behavior and ideation. The Baseline/Screening version will be administered at Visit 1 and the Since Last Visit version will be administered at Visits 2, 3, and 4/ET. 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).

### **6.2.2.9 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 (pre-dose only), Visit 3, 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 Pharmacokinetic Assessments**

Plasma concentrations of midazolam and 1-hydroxymidazolam will be determined using a bioanalytical assay in a GLP analytical laboratory contracted by the study sponsor. Blood samples for PK analyses will be collected from each subject before and at 5, 10, 20, 30 minutes, and 1, 2, and 4 hours after administration of the first test dose at Visit 2. After 132 subjects have completed the Comparative Phase, for all new test dosed subjects, blood samples for PK analyses will be collected from each subject before and at 5, 10, 20, 30 minutes, and 1 hour after administration of the first test dose at Visit 2.

Blood samples will be collected through a saline flush catheter or by direct venipuncture using Vacutainer<sup>®</sup> or Monovette<sup>®</sup> 6 mL tubes containing EDTA K2 anticoagulant and will immediately be placed in an ice bath. The clock times of all blood draws will be recorded and reported for each subject. All tubes will be labeled with the subject number, protocol, visit number, and planned blood draw time point. A maximum of 50 mL of blood will be collected for PK analysis during the entire course of the study. Following collection (maximum 110 minutes), the blood samples will be centrifuged at 4°C with a centrifugal speed of approximately 3000 rpm for 10 minutes. Plasma will be split into 2 aliquots of at least 1.0 mL each and placed in labeled, screw-cap, polypropylene tubes. Labels will be affixed to the tubes in a manner that will prevent detachment after freezing. All plasma PK samples will be stored frozen at -20°C (±5°C), within 120 minutes from the start of centrifugation until they are shipped to the analytical laboratory.

Bioanalytical samples will be transported to the analytical laboratory in 2 separate shipments, with each set of aliquots in separate shipments. Once the analytical laboratory confirms receipt of the first shipment, the second set of aliquots may be sent. The samples should be packed on sufficient dry ice to be kept frozen for at least 72 hours.

Detailed instructions for PK sample collection, storage, and shipping will be provided by the analytical laboratory.

#### **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.

#### **6.2.5 Subject and Caregiver Outcome Assessments**

The subject and caregiver outcome assessments should be completed at each visit as 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.

##### **6.2.5.1 SF-12v2 Health Survey (SF-12)**

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 the primary caregiver individually at Visits 2 and 4.

##### **6.2.5.2 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 Visits 2 and 4.

##### **6.2.5.3 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 primary caregiver individually at Visit 4.



#### **6.2.5.4 Caregiver Questionnaire**

The Caregiver Questionnaire is self-administered by the primary caregiver and consists of 2 main sections as follows: 1) Caregiver demographics (completed at Visit 2 or if there is a change in primary caregiver during the study), and 2) Resource utilization (completed at Visit 4). The purpose of the resource utilization questions is to capture any unscheduled healthcare use that occurred as a result of the seizure activity for which the study drug was administered.

### **6.3 Prior and Concomitant Therapy**

Prior therapy is defined as any medication (prescription or non-prescription), nutritional supplement, herbal preparation or device (e.g. VNS magnet) taken or used within 30 days prior to the first dose of study drug at Visit 2.

If the subject is using or has recently used any of the food, beverage, or medicinal products listed in [Appendix 1](#), Prohibited Concomitant Substances, 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 2 through Visit 4 or ET.

#### **6.3.1 Permitted Medications**

A subject's AED regimen (with or without intermittent use of benzodiazepines at a constant dose [see [Section 6.3.3](#)]) must be stable (no changes in drug type) from Visit 1 through Visit 4 or ET and for  $\geq 7$  days before Visit 2. Changes in dose of an AED are allowed during the study, however, the new dose level must be kept stable for at least 7 days before the subject receives study drug in both the Test Dose and Comparative Phases. VNS settings must be kept stable throughout the study period and the use of a magnet with the VNS must 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 Medications**

The medications listed in [Appendix 1](#), Prohibited Concomitant Substances are prohibited from Visit 1 through Visit 4 / ET. These medications include CYP450 3A inhibitors/inducers, opioids, and other respiratory depressants (except antiepileptic drugs). If a subject was taking any of these medications at or before Visit 1, the time between the last dose of that substance and Visit 2 must be equal to or greater than the minimum washout time shown in [Appendix 1](#), Prohibited Concomitant Substances.

If a subject takes any of these medications after V2 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  $\leq 3$  days in a 7-day period on average and always at the same dose. 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; this will be outlined in the subject's PMP.

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**

Food and beverage substances that are restricted during this study are detailed in [Appendix 1](#), Prohibited Concomitant Substances. Foods and beverages not permitted during the study (from Visit 1 to Visit 4) include grapefruit, grapefruit juice, Seville oranges, and star fruit. Consuming these substances during the study may alter the subjects' response to treatment with USL261. 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 their future medical care. The investigator will also discontinue a subject's study participation if the subject has not treated a seizure cluster meeting the study criteria within 6 months after randomization. A subject who prematurely discontinues from the study should return to the clinic within 7 days to undergo the ET visit (Visit 4) 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:** The subject findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., change in AED drug during the study, 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 randomization**
- **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

***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 Visit 4 evaluations. In the event that a subject elects not to return to the study site 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.

***Replacement of Subjects:***

Subjects who prematurely discontinue from the study after receiving double-blind study drug will not be replaced.

**6.6 Treating Overdose**

Refer to the Hospira Midazolam Injection, USP, Package Insert for full details on midazolam overdose (see [Appendix 2](#)). In the case of suspected overdose, respiration, pulse rate, 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 access should be obtained. 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 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 AE(s) 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 (Visit 4) evaluations. The investigator must notify USL or its designee within 24 hours of learning about the pregnancy. The investigator must complete the Pregnancy Notification Form provided by USL or its designee. The investigator 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 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:

- 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 serious AE (SAE).

- **Seriousness:** As provided in FDA Title 21 CFR Part 312 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 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 (Visit 4 [Post-Dose Assessment or ET]) 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 or SAE 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 (Visit 4 [Post-Dose Assessment or ET]) 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 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 as described below. 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 the Medical Monitor.

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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 serious event. 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](#).

any extensions or variations thereof.

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**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	Immediate but no later than 1 business day	E-mail or Fax the SAE report form[a]	<p><b><u>United States and Canada:</u></b> Email: SAEReportingUS@pharmanet-i3.com Fax #: +1-609-951-6670</p> <p><b><u>Rest of World:</u></b> Email: SAEReportingUS@pharmanet-i3.com Fax #: +44-1628-461141</p>
Fatal or Life-Threatening SAEs	Immediate	Telephone or E-mail[b]	<p><b><u>North and South America:</u></b> [REDACTED] (e-mail)</p> <p><b><u>Rest of World:</u></b> [REDACTED] (e-mail)</p>
	Immediate but no later than 1 business day	E-mail or Fax the SAE report form[a]	<p><b><u>United States and Canada:</u></b> Email: SAEReportingUS@pharmanet-i3.com Fax #: 1-609-951-6670</p> <p><b><u>Rest of World:</u></b> Email: SAEReportingUS@pharmanet-i3.com Fax #: +44-1628-461141</p>

[a] Email 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/EC.

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 fully investigate 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 preexisting 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**

At Visit 1, the investigator, or designee, will contact the Interactive Response Technology System (IRT) to register the subject. At Visit 2, the investigator, or designee, will contact IRT to confirm the administration of the test dose. At Visit 3, subjects meeting the eligibility criteria will be randomized (2:1) to receive USL261 or matching placebo using the IRT; the Investigator, or designee, will obtain a drug kit number via IRT at Visit 3. Instruction on access and use of the IRT service will be detailed in the IRT manual provided by the IRT vendor.

The randomization code will be generated by an unblinded statistician at the CRO [inVentiv Health Clinical] who is not otherwise involved in study activities. The randomization will

be generated using fixed blocks and will be stratified by age (< 18 vs. ≥ 18). USL will not have access to the randomization code.

## 8.2 Blinding

USL261 will not be blinded for the Test-Dose Phase or for the second dose provided to some subjects during the Comparative Phase; however, blinding is considered important for safety and efficacy assessments for the first dose of the Comparative Phase. Therefore, drug supplies for the first dose in the Comparative Phase will be labeled in double-blind fashion with information including the protocol number, kit identification number, and instructions for use. The drug name will not appear on the label, and neither the investigator/study center staff nor the subject/caregiver will know the identity of the randomized medication. The interim analyses will be conducted by an unblinded statistician and reviewed by an unblinded interim monitoring committee, both independent of the sponsor. The sponsor, USL, will remain blinded throughout the trial until database lock has occurred. Once database lock has occurred, the final statistical analysis of this trial will be performed by a CRO under the direction of USL.

If it is medically imperative to know what study treatment the subject is receiving, the investigator or designee will contact the IRT and select the option for exposing the blinded information. The individual who breaks the blind must record the date and rationale in the subject's medical records and on the eCRF. In such cases, the investigator or designee should contact the Medical Monitor before the blind is broken (if possible). Every effort should be made to collect complete efficacy and safety data on these subjects. Furthermore, inVentiv Health Clinical will also have the capability to unblind individual subject data for the purposes of fulfilling regulatory reporting requirements for unexpected AEs, which is in compliance with ICH guidelines.

## 9 MATERIALS AND SUPPLIES

### 9.1 Study Drug

USL261 contains midazolam, EP/USP, as the active ingredient, and the inactive ingredients

[REDACTED]

USP. 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.

Midazolam, the active ingredient in USL261, is designated as a Schedule IV controlled substance with abuse potential by the US Controlled Substances Act (21 CFR §1308).

The placebo nasal spray will consist of the same inactive ingredients as found in the USL261: [REDACTED]

[REDACTED] Each actuation of the unit dose pump will deliver 0.1 mL of this solution.

#### 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 and placebo nasal spray containers will be provided as ready-to-use assemblies packaged to prevent accidental actuation. Both active and placebo drug utilize 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 (active and placebo) 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.

The study drug supplies will be labeled appropriate to their use. USL261 5.0 mg containers for the Test Dose Phase and the second dose of the Comparative Phase will be identified as open-label treatments. The label for the double-blind, first dose of the Comparative Phase will contain at a minimum the following information for the US (additional items will be added as required for other study countries):

- Protocol number
- Kit identification number from the randomization scheme
- 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**

An individualized PMP will be prepared by the investigator or designee for each subject based on information provided by the subject (when able) and caregiver(s).

The individualized PMP will describe, at a minimum, the type of seizure cluster eligible for treatment with study drug, the criteria for seizure cluster recognition, when to administer the study drug, when to call the central study nurse hotline, requirements for when to give the second dose of study drug (ie, 5.0 mg dose of USL261), and a rescue protocol for persistent



or recurrent seizure activity or other safety concern. Contact information for study center personnel, the central study nurse hotline and emergency medical service(s) will also be listed in the PMP.

The following steps will be followed for PMP preparation:

1. At Visit 1, the subject and caregiver each provide the investigator (or designee) a description of both the seizure clusters and the typical, non-clustering seizures (if any) in their own words.
2. The investigator (or designee) will add his/her notes to the subject and caregiver descriptions, specifying what type of seizures each description refers to and any other relevant information.
3. The PMP is drafted by the investigator and qualified study center personnel using the template provided by the Sponsor or CRO.
4. The PMP, including the seizure cluster descriptions from the subject, caregiver, and investigator, are then provided to an expert Central Reviewer for a final determination of whether or not the subject qualifies for study inclusion and input on whether further information is needed.
5. The PMP is finalized by the investigator and qualified study center personnel before the subject receives the first test dose at Visit 2. The PMP will be discussed and agreed upon by the subject, caregiver, and investigator.
6. Subjects and caregivers will receive a copy of the PMP at Visit 3. A summary of the PMP (i.e., laminated card for convenient reference) will also be provided.

If the Central Reviewer does not approve the subject for study participation, the subject will be screen failed.

### **9.3.2 Subject Workbook**

Caregivers will receive a Subject Workbook for the Comparative Phase of the trial. In this study, the Subject Workbook is a critical source document for collecting and recording

outpatient information during the Comparative Phase of this study. The Subject Workbook will be used to record:

- Seizure activity (Seizure activity 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 [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 subject's or caregiver's ability. The caregiver will document in the Subject Workbook all seizure activity that occurs from the time the subject and caregiver receive the study materials kit at Visit 3 until Visit 4 or ET).
- 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
- 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 Visit 4 or ET.

At Visit 2, the caregiver will enter timed respiration rate measurements into a practice Subject Worksheet for training purposes (see [Section 9.3.3](#)).

### 9.3.3 Caregiver Training Materials

Caregivers will be trained in study procedures by qualified study personnel beginning as early as Visit 1 and retrained, if necessary, at Visits 2 and 3. Training will be provided to the caregiver(s) at Visit 1 for self-study on the following topics:

- Overview of the study
- Understanding the subject's individualized PMP
- Recognizing a cluster seizure episode
- Procedures for study drug administration
- Mandatory requirement for contacting the central study nurse after subject is treated with double-blind study drug and the second dose of study drug (i.e., 5.0 mg dose of USL261), if needed
- Performing study-related measurements (e.g., measuring respiration rate, completing the Subject Workbook)
- Procedures for safety monitoring
- Cardiopulmonary resuscitation (CPR) including airway management
- Contact information for help and advice from study center personnel and a toll-free telephone hotline to a central study nurse (available 24 hours a day, 7 days a week)

The training provided at Visit 1 for self-study will be completed at or before Visit 2. Completion of the self-study training will be certified by qualified study staff and/or by web-based or paper-based questionnaire. The investigator, or other qualified study personnel, will review, assess, and (if needed) re-instruct subjects and caregivers on the information provided in the self-study training at Visits 2 and 3. Before subjects are given the test dose at Visit 2, caregivers must pass the CPR exam, which addresses airway management, breathing, and circulation and must demonstrate airway management techniques including neck extension, chin lift, and jaw thrust maneuvers. During Visit 2, the primary caregiver will administer the second test dose and monitor the subject by performing timed respiration rate measurements. Respiration rate assessed by the caregiver will be recorded in a practice Subject Worksheet at Visit 2.

Before the subject is randomized, caregivers must have demonstrated hands-on competence in administering the study drug, performing the timed respiration rate measurements, recording information in the practice Subject Worksheet, and performing the correct technique for airway management. The investigator or his/her designee will confirm that the subject and caregiver clearly understand the study procedures (e.g., requirements for documenting seizure activity, timing for respiration rate monitoring, etc.) before leaving the study center at Visit 3.

Caregivers that are added during the study will have to complete similar training requirements as those noted above.

#### **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 site receives, and document any damaged or unusable study drug in the inventory log.

Only after receipt of all required documentation from a clinical site 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 and forward the original to the drug distribution center. 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 code) 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 securely locked, substantially constructed enclosure with limited access (e.g., locked cabinet). The investigator will take adequate precautions to prevent theft or diversion of the study medication, consistent with 21 CFR § 312.69. Within the locked storage area, study drug will be stored at a controlled room temperature (with excursions between 15° and 30°C [59° and 86°F]) until used.

Before an investigator is allowed to participate in this study, the drug storage area at his/her site 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 medication will be dispensed by the study center pharmacist or other qualified individual, and each test dose or study drug kit dispensed will be documented in the drug accountability log.

The USL261 test doses (2 USL261 5.0 mg containers) will be dispensed to study personnel at Visit 2.

If the subject continues to meet all eligibility criteria at Visit 3, the pharmacist or other qualified individual at the study center will call the IRT to obtain the kit identification number. The appropriate study drug kit, which contains blinded study drug and the second dose of study drug (i.e., 5.0 mg dose of USL261), will then be documented and dispensed to

the subject or caregiver. When dispensing the study drug kit at Visit 3, qualified site personnel will also tell or remind subjects/caregivers to:

- Store study drug at controlled room temperature (see [Section 9.4.1](#)), and
- Return study drug containers, both used and unused, to clinic staff at the next visit

### **9.4.3 Return or Destruction of Study Drug**

At Visit 4 or ET, 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, a final inventory of study drug shipped to the site, dispensed, and remaining at the site will be performed by the Study Monitor (or designee) and the investigator (or designee). This reconciliation will be logged on the drug accountability form, signed, and dated. If any supplies are missing, this must be indicated on the drug accountability/return forms along with an explanation of the discrepancy. Any discrepancies noted will be investigated, resolved, and documented before 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 or designee, 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 drugs will be returned to USL or designee for destruction.

## **10 DATA ANALYSIS AND STATISTICAL PROCEDURES**

All statistical analyses will be performed using appropriate procedures in SAS version 9.2 or higher. Additional software may be used for the production of graphics or specific statistical methodology as appropriate.

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

Statistical significance will be determined by two-sided tests with p-value <0.05, unless otherwise specified.

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 and unblinding.

## 10.1 Populations for Analysis

**Screened Population:** The Screened Population includes all subjects who signed an ICF or assent form.

**Safety Population:** The Safety Population includes all subjects who received at least 1 dose of study drug. Therefore, this population includes all treated subjects, including those who terminate before randomization, as well as all subjects who are randomized.

**Randomized Population:** The Randomized Population contains all subjects who are randomized to receive double-blind treatment.

**Modified Intent-to-Treat Population (mITT):** The mITT Population will consist of all subjects in the Randomized Population who receive at least 1 dose of study drug during the Comparative Phase and who have any post-treatment efficacy assessments.

**PK Population:** The PK population contains all subjects who receive both test doses of USL261 in the Test-Dose Phase with sufficient blood samples for PK analysis.

## 10.2 Disposition, Demographics, and Other Baseline Characteristics

A summary of subject disposition will be prepared that displays the number of subjects screened, and the number of subjects who received a test dose, were randomized, who received double-blind study drug in the Comparative Phase (first dose), who received the

second dose of study drug (i.e., 5.0 mg dose of USL261) in the Comparative Phase, and who completed the study. The number of subjects who did not complete the study will be summarized according to the primary reason for withdrawal. The number of subjects in each analysis population will also be tabulated.

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

### **10.3 Medical and Surgical History**

Medical and surgical history will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>) and the incidences will be tabulated for the Safety Population.

### **10.4 Prior and Concomitant Medications**

All medications will be classified according to the World Health Organization Drug Dictionary and the incidences will be tabulated by drug class and/or generic name for the Safety Population during the Test Dose Phase and for the Randomized and Randomized Safety population during the Comparative Phase. Prior medications will include all medications taken 30 days prior to the first dose of study drug. Prior medications will be summarized for the Randomized and Randomized Safety populations. Concomitant drug therapy will include all medications (prescription or non-prescription), nutritional supplement, or herbal preparation taken from Visit 2 through Visit 4 or ET. Concomitant AEDs will be summarized separately.

### **10.5 Efficacy Analyses**

The data to assess the efficacy endpoints will be obtained from the Subject Workbooks and entered into the Electronic Data Capture (EDC) system. All efficacy analyses will be conducted using the mITT Population, and analyzed according to the randomized treatment assignment.



### **10.5.1 Primary Efficacy Endpoint and Analysis**

The primary efficacy endpoint is the proportion of subjects who meet the criteria for Treatment Success. Treatment Success is a composite measure of efficacy that will be assessed based upon the first seizure cluster treated with study drug during the Comparative Phase. Treatment Success is defined as achieving the following:

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

Subjects who receive the second dose of study drug within 6 hours of the first dose during the Comparative Phase (i.e., USL261 5.0 mg) will not meet the definition of Treatment Success.

The null hypothesis is that there is no difference in the proportion of subjects with Treatment Success in the USL261 and placebo groups. The alternative hypothesis is that the Treatment Success rate will be different between the USL261 and placebo groups.

The primary efficacy endpoint will be analyzed by Fisher's Exact Test using the mITT Population. The 95% confidence intervals (CIs) around the proportions will be reported. Chi-squared test will be performed as a sensitivity analysis.

The components of the primary endpoint (seizure termination and recurrence) will also be analyzed separately using Fisher's Exact Test.

Additional exploratory analyses may be conducted; details will be provided in the SAP.

#### **10.5.1.1 Missing Data and Sensitivity analysis for Primary Outcome**

Subjects who do not have sufficient available data to confirm whether they can be classified either as "Treatment Success" or as "Not a Treatment Success" are considered to have missing data. Subjects with missing data impacting determination of Treatment Success will be assumed to have had an unfavorable outcome and will be treated as not a Treatment Success.

Sensitivity analysis will be conducted for the Treatment Success endpoint in order to assess robustness of study conclusions to missing data using a tipping point approach.

### 10.5.2 Secondary Efficacy Endpoints and Analyses

The secondary efficacy analyses will be performed on the mITT population. The secondary efficacy endpoints include the following:

- Proportion of subjects with recurrence of seizure(s) beginning 10 minutes after administration of double-blind study drug to 4 hours after administration of double-blind study drug
  - Subjects who have been administered the second dose of study drug (i.e., 5.0 mg dose of USL261) within 4 hours of double-blind study drug administration will be assumed to have had a seizure.
  - The proportion of subjects with occurrence of seizure(s) within 4 hours after administration of study drug will be analyzed using Fisher's Exact Test. The 95% CIs will be presented for the proportion. In addition, Chi-squared test will be performed as a sensitivity analysis.
- Time to next seizure with a start time > 10 minutes after study drug administration
  - Subjects who do not have another seizure before the end of the 24-hour observation period, and have not been administered the second dose of study drug (i.e., 5.0 mg dose of USL261) will be censored at the end of the observation period.
  - Subjects administered the second dose of study drug (i.e., 5.0 mg dose of USL261) that did not have a seizure before the administration of second dose of study drug (i.e., 5.0 mg dose of USL261) will be censored at the time of the second dose (USL261) administration.
  - This variable will be analyzed by a log-rank test, and presented with Kaplan-Meier estimates for time-to-event at specific percentiles with associated standard error and 95% CI. The Kaplan-Meier curve will be displayed by treatment arm.

In addition, the hazard ratio for treatment (USL261: placebo) and its 95% CI will be calculated from a Cox proportional hazards model.

### 10.5.3 Exploratory Efficacy Variables and Analyses

Exploratory efficacy variables and analyses are detailed below and will be analyzed using the mITT population.

- Proportion of subjects with recurrence of seizure(s) beginning 10 minutes after double-blind study drug administration to 24 hours after double-blind study drug administration
  - Subjects who have been administered the second dose of study drug (i.e., 5.0 mg dose of USL261) within 24 hours of double-blind study drug administration will be assumed to have had a seizure.
  - The proportion of subjects with occurrence of seizure(s) within 24 hours after administration of study drug will be analyzed using Fisher's Exact Test. The 95% CIs will be presented for the proportion. In addition, Chi-squared test will be performed as a sensitivity analysis.
- Return to full baseline functionality within 24 hours after study drug administration (as determined by the caregiver)
  - Subjects who do not return to full baseline functionality by the end of the 24-hour observation period, and have not been administered the second dose of study drug (i.e., 5.0 mg dose of USL261), will be censored at the end of the observation period.
  - Subjects who were administered the second dose of study drug (i.e. 5.0 mg dose of USL261) will be censored at the time that the second dose of study drug (i.e., 5.0 mg dose of USL261) was administered.
  - The proportion of subjects who have documented return to full baseline functionality will be analyzed by Fisher's Exact Test. The 95% CIs will be presented for the proportion. In addition, Chi-squared test will be performed as a sensitivity analysis.
  - This variable will be analyzed by a log-rank test, and presented with Kaplan-Meier estimates for time to event at specific percentiles with associated

standard error and 95% CI. The Kaplan-Meier curve will be displayed by treatment arm. In addition, the hazard ratio for treatment (USL261: placebo) and its 95% CI will be calculated from a Cox proportional hazards model.

- Analyses for subjects receiving 2 doses of study drug (see [Section 10.5.3.1](#))
- Subject and caregiver outcome assessments

### 10.5.3.1 Analyses for Subjects Receiving 2 Doses of Study Drug

It is important to assess the subject's response to the second dose of study drug (i.e., 5.0 mg dose of USL261) in order to evaluate the usefulness of the split-dose strategy. Data from subjects randomized to receive double-blind USL261 and who subsequently received the second dose of study drug (i.e., 5.0 mg dose of USL261) will be analyzed to determine:

- The proportion of subjects who satisfy the Treatment Success criteria relative to the timing of the second dose of study drug (i.e., 5.0 mg dose of USL261); the analysis and definition of Treatment Success will be similar to the primary efficacy variable described in [Section 10.5.1](#).

### 10.5.4 Safety Analyses

Safety will be assessed through the collection of AE reports, OAA/S (Sum and Composite scores), requirements for unscheduled ER or EMS visit(s), vital signs, caregiver-recorded respiration rates, laboratory evaluations, ECGs, physical, nasal and neurological examinations, and C-SSRS scores. All safety analyses will be presented by phase of the study based on the Safety Population and Randomized Safety Population, unless otherwise specified.

Safety data from both the Test-Dose Phase and the Comparative Phase will be summarized.

**Adverse Events:** AE verbatim text will be coded using MedDRA and summarized by System Organ Class (SOC) and preferred term. AEs with onset on or after the start of study drug and up to 7 days after the last dose of study drug are considered treatment emergent

adverse events (TEAEs); AEs reported prior to treatment administration in the Test-Dose Phase will be included in subject listings but not included in summaries.

Patients who experience at least 1 TEAE or SAE will be presented for each SOC and preferred term by treatment received. 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). SAEs and AEs leading to discontinuation will be summarized. In addition, listings of all TEAEs, SAEs, and AEs leading to discontinuation will be presented.

**Clinical Laboratory Data:** Clinical laboratory results for serum chemistry, hematology, and urinalysis will be presented by treatment received and visit using summary statistics. Changes from baseline will also be displayed. Normal range shift tables will be generated for each parameter. In addition, clinically significant abnormalities, as predefined in the SAP, will be tabulated.

**Vital Signs Measurements:** Vital signs measurements performed by study site staff will be presented using descriptive statistics. Systolic and diastolic BP (mmHg), HR (bpm), RR (breaths per minute), and temperature (degrees Celsius) will be summarized at each visit and time point. Changes from baseline will also be displayed.

**Caregiver-recorded respiration rate:** Caregiver-recorded respiration rates will be presented using descriptive statistics at each time point by treatment group and overall total for Randomized safety population. 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, treatment group, and overall total.

**ECG Measurements:** For 12-lead ECG parameters, changes from baseline (Visit 2; pre-dose) to post-administration of first test dose (Visit 2; 15 minutes post-dose) for all subjects will be summarized descriptively at each scheduled visit and time point collected for the Safety Population. Mean and mean change from baseline values at Visit 2 will be presented. In addition, counts and percentages for ECG diagnosis (normal or abnormal) at each study visit and time point will also be presented. If the diagnosis was abnormal, counts and

percentages for clinical significance will be presented. The number of subjects meeting the criteria specified in SAP will be presented by treatment group for the Safety Population.

**OAA/S Composite and Sum Score:** Both the Sum and Composite scores for the OAA/S will be presented by time point at Visit 2. The OAA/S Sum score is calculated as the sum of the scores in the 4 assessment categories. The Sum score will be set to missing if 1 or more of the 4 assessment categories are missing. The OAA/S Composite score is the lowest score among the 4 assessment categories. The Composite score will be set to missing if all 4 of the assessment categories are missing. Descriptive statistics and graphical presentations will be used to present results by time point at Visit 2 for the Safety Population. Number of subjects with an OAA/S composite score of 1 at Visit 2 will be presented by time point and overall.

**Requirement for Unscheduled ER or EMS Visit:** The number of subjects requiring an unscheduled EMS or ER visit within 24 hours after study drug administration during the Comparative Phase will be compared between treatment groups for the Randomized Safety Population using Fisher's Exact Test. In addition, Chi-squared test will be performed as a sensitivity analysis.

**C-SSRS:** C-SSRS results will be summarized at each visit. The number and percent of patients with each suicidal behavior and ideation will be displayed. The number and percent of patients with any suicidal behavior and any suicidal ideation, along with the number and percent of patients 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.

**Physical, nasal and neurological examinations:** For physical, nasal and neurological 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 by treatment group and visit.

**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.

### **10.5.5 Data and Safety Monitoring Board**

The DSMB will meet to review safety data for the first 25 subjects who have completed the Test-Dose Phase and when approximately 33, 66, 99, 132, 165, and 204 subjects have Comparative Phase data available. The DSMB may also decide to meet and review safety data at other time points deemed necessary.

All analyses that are required to support the DSMB will be performed by an unblinded statistician not otherwise involved in the study. The DSMB will notify the Sponsor's Senior Management of the results only if they recommend discontinuing the trial due to safety-related reasons. Even then, the Sponsor will not have access to individual subject data until after the database is locked.

Details of the DSMB membership, meeting schedule, and data review and analysis will be documented in the DSMB Charter.

## **10.6 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses**

### **10.6.1 Pharmacokinetic Variables and Analyses**

Pharmacokinetic parameters for individual plasma concentrations will be calculated using a standard non-compartmental approach using appropriate validated pharmacokinetic software (WinNonlin Enterprise version 5.2 or higher). The following PK parameters of midazolam and 4-hydroxymidazolam will be calculated from data obtained for the PK Population:

- $AUC_{0-t}$  – the area under the plasma concentration-time curve (AUC) from time 0 to time t, where t is the last measurable concentration, estimated using the linear trapezoidal rule
- $AUC_{0-inf}$  – the AUC from time 0 extrapolated to infinity, calculated by adding  $C_t/\lambda_z$  to  $AUC_{0-t}$ , where  $C_t$  is the last quantifiable concentration and  $\lambda_z$  is the elimination rate constant

- $C_{\max}$  – the maximum plasma concentration
- $t_{\max}$  – the time to reach the maximum plasma concentration
- $\lambda_z$  – the terminal elimination rate constant
- $t_{1/2}$  – the terminal elimination half-life
- $t_{\text{lag}}$  – the time before the first measurable plasma concentration
- $CL/F$  – apparent clearance\*
- $V_{\beta}/F$  – volume of distribution\*

\* calculate for Midazolam only and not for 1-OH-midazolam.

Concentrations values reported as below the limit of quantification (BLQ) will be treated as “0” and listed as BLQ. For the calculation of PK parameters, BLQ values will be set to zero (“0”). Actual sampling times will be used in the calculations of pharmacokinetic parameters.

Descriptive statistics will include the number of observations, mean, geometric mean, standard deviation (SD), and coefficient of variation, as well as median, minimum, and maximum for the PK variables. Additional descriptive statistics will be provided by subgroup such as age group, gender, race, etc. Exploratory analysis assessing the relationship between PK parameters and selected baseline characteristics may be conducted if applicable.

### 10.6.2 Pharmacokinetic/Pharmacodynamic Variables and Analyses

The PK/PD analysis of data from the test dose will consist of correlating the plasma midazolam plus 1-hydroxymidazolam concentrations to respiratory rate, BP, HR, O<sub>2</sub> saturation, and sedation based on OAA/S scores. Regression analysis will describe the PK/PD relationship, if one exists. If appropriate, for those PD measurements found to correlate to plasma concentrations, the influence of covariates such as gender, AED inducer status, weight, BMI, race, and age group will be explored.

### 10.7 Sample Size Justification

Recently, a well-controlled study of IM diazepam (DZP) for the treatment of acute repetitive seizures was reported in the literature (See [Table 6](#) below).[42] A meta-analysis based on



Odds Ratio was conducted on the pooled data from this recent study and the two well-controlled studies of rectal (PR) Diazepam-Diastat that were used as the basis for the original design of this protocol (see Table 6 below).[43, 44]

**Table 6. Well Controlled Trials Reported in the Literature**

Reference Study	Treatment	Placebo Response	Treatment Response
Abou-Khalil et al. 2013 [42]	IM Diazepam	0.50	0.72
Cereghino et al., 1998 [43]	PR Diazepam-Diastat <sup>b</sup>	0.40	0.63
Dreifuss et al, 1998 <sup>a</sup> [44]	PR Diazepam-Diastat <sup>b</sup>	0.28	0.64

a) In this study sequential doses were administered at the onset of seizure, 4 hours (children and adults) and 12 hours (adults only) post first dose. Therefore, only the data out to 4 hours post first dose was used.

b) Response rates were extracted from Kaplan-Meier curves.

In this meta-analysis the outcomes from the three different studies are relatively consistent with an estimated pooled common Odds Ratio of 2.90, which is significantly lower than 3.5 assumed Odds Ratio in the original protocol. With the originally planned sample size of 132 subjects who have completed the Comparative Phase the power is estimated to be 75%, much lower than the targeted 90% power. Therefore, a classic group sequential design, with 3 interim analyses and a maximum sample size of 240 subjects who have completed the Comparative Phase is proposed in order to reach sufficient overall power (approximately 90%) for this study with possible study stopping at interims for efficacy or futility.

In this group sequential design, interim analyses will occur after 132, 165, and 204 subjects have completed the Comparative Phase. At any interim analysis the trial may stop early for either efficacy or futility. Assuming a 0.40 placebo rate with the updated odds ratio of 2.9, the overall power of this design is approximately 90%, while maintaining 2.5% type I error. All interim analyses will be performed using the mITT population and a one-sided test comparing two proportions. Interim analyses will be conducted by an unblinded statistician and reviewed by an unblinded Interim Analysis Monitoring Committee (IAMC), both independent of the sponsor. IAMC membership, responsibilities, timelines, and communication channels will be clearly specified in a charter. In particular, the IAMC

communication channels with the sponsor will be limited to maintain the blind of the sponsor study team in order to minimize the chance of operational bias. To this end, the IAMC will inform senior management first of the decision to continue the trial or stop according to the statistical analysis plan. Senior management will in turn inform the team to continue or not to continue the study only with no further information on the interim analysis.

In order to achieve the maximum sample size of 240 subjects who have completed the Comparative Phase, 350 subjects will be enrolled in the Test-Dose Phase to account for the approximate 32% of subjects test dosed that do not complete the requirements for efficacy evaluation (receive at least 1 dose of study drug during the Comparative Phase and who complete Visit 4).

### **10.8 Interim Analyses for Success**

At the sample sizes of N=132, 165, 204, and 240 subjects completing the Comparative Phase, a one-sided test of two proportions is performed to determine the test value to compare to the critical value obtained from a Lan-DeMets alpha spending function approximating a Pocock boundary. Complete details for the critical values at each interim analysis and simulation results are provided in the SAP.

### **10.9 Interim Analyses for Futility**

At each of the prespecified interim analyses (N=132, 165, 204, futility is not applicable at the N=240 final analysis) the predictive probability of success at the maximum sample size is computed. This calculation begins by assuming uniform prior distributions Beta (1,1) on probability of treatment success in the control arm ( $p_C$ ) and the probability of treatment success in the treatment arm ( $p_T$ ) and computing the posterior distribution with the currently available data. The predictive distribution of the final data assuming the maximal sample size of N=240 is then computed. The number of future treatment successes for each arm has a Beta-Binomial distribution which is then added the fixed number of current treatment successes in each arm. We may then compute the predictive probability that a trial success is reached at N=240 subjects completing the Comparative Phase. If this predictive probability is less than 10%, the trial will be stopped for futility. Note that the success

boundaries are computed assuming no futility stopping, and thus controls type I error regardless of the method used for futility stopping. Complete details and simulation results are found in the SAP.

## **11 ADMINISTRATIVE PROCEDURES**

### **11.1 Regulatory Approval**

This study requires application to the appropriate regulatory body 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 bodies 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 (IRB) or Independent Ethics Committee (IEC) Approval**

USL or its designee must receive signed and dated written confirmation that the study protocol and ICF and assent forms 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 before 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 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 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 clinic- 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 represents 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) has therefore 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., hospital and general practice charts, appointment books, original laboratory records). The investigator must exercise judgment regarding information in a subject's chart that is not relevant to the performance, observations, or conduct of this study. 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.

### **11.6.1 Data and Safety Monitoring Board**

The study will be conducted under the supervision of an independent DSMB (see [Section 10.5.5](#), Data and Safety Monitoring Board). All DSMB members have extensive experience in either clinical trials and/or management of seizures. The DSMB is responsible for the ongoing review of a clinical trial and for making recommendations concerning the continuation, modification, and termination of the trial.

## 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:

- 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 representatives 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 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, formulae, 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 or permission granted by USL. In accordance with generally recognized principles of scientific collaboration, coauthorship 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 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.

### **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. Minor deviations may appear to be of

little or no consequence, but nonetheless they should be reported so that they can be assessed for their effect on the 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 disclosure statements 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 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 Visit 4 / ET. If the subject was taking any of these medications at or before Visit 1, the time between the last dose of that substance and Visit 2 must be equal to or greater than the minimum washout time shown below.

The first listing 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 of substances represents opioids, or 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 the usage is unlikely to achieve meaningful systemic levels. **These lists may not be all-inclusive**; direct any questions to the Medical Monitor.

### Listing 1:

	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	<i>Bergamottin (a constituent of grapefruit juice)</i>	----	7
C	Chloramphenicol	Alficytyn, Amphicol, Biomicin, Chlornitromycin, Chlora, Phenicol, Medicom, Nevimycin Vernacetin, Veticol	7
	Cimetidine	Tagamet	7
	Cyclosporine	Gengraf, Neoral, Sandimmune	7
	Cisapride	Propulsid	7
	Clarithromycin	Biaxin, Biaxin XL	7



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<b>D</b>	Danazol	Danocrine	7
	Delavirdine	Rescriptor	7
	Diethyldithiocarbamate (diethyldione, diethyldithiocarbamic acid)	—	7
	Diltiazem	Cardizem, Tiazac, Dilacor XR	7
<b>E</b>	Echinacea	—	7
	Efavirenz	Efavirenz	11
	Ergotamine	Cafergot	7
	Erythromycin	Robimycin, E-Mycin, E.E.S. Granules, E.E.S.-200, E.E.S.-400, Filmtab, Erymax, Ery-Tab, Eryc, Ranbaxy, Erypar, EryPed, Eryped 200, Eryped 400, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Zineryl, Abbotcin, Abbotcin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	7
<b>F</b>	Fluoxetine	Prozac, Fontex, Ladose, Sarafem, Solax, Lovan	30
	Fluvoxamine	Luvox	7
<b>G</b>	Gestodene	Minesse	7
	<i>Grapefruit</i>	—	7
	<i>Grapefruit juice</i>	—	7
<b>I</b>	Imatinib	Gleevec	7
	Indinavir	Crixiban	7
	Itraconazole	Sporanox	7
<b>K</b>	Ketoconazole	Nizoral	7
<b>L</b>	Lovastatin	Mevacor	7
<b>M</b>	Metronidazole[a]	Flagyl	7
	Mibefradil	Posicor (withdrawn from US market)	7
	Miconazole[a]	Monistat	7
	Mifepristone	Mifeprex	7
<b>N</b>	Nefazodone	Serzone	7
	Nelfinavir	Viracept	7
	Nevirapine	Viramune	9
	Nisoldipine	Sular	7

	Nitrendipine	Bayotensin, Baypress, Bylotensin, Deiten, Nidrel, Nitrepin	7
	Norfluoxetine (metabolite of fluoxetine)	—	30
<b>Q</b>	Quinidine	Quin-Release, Quinaglute Dura-Tabs, Quinidex Extentabs	7
<b>R</b>	Rifabutin	Mycobutin	13
	Rifampin	Rifadin	7
	Ritonavir	Kaletra, Norvir	7
<b>S</b>	Saquinavir	Fortovase, Invirase	7
	<i>Seville oranges</i>	—	7
	<i>Star fruit</i>	—	7
	St. John's Wort	—	30
<b>T</b>	Tacrolimus	FK506, Prograf	8
	Telithromycin	Ketek	7
	Thalidomide	Thalomid	7
	Troleandomycin	Tao	7
<b>V</b>	Verapamil	Calan, Isoptin	7
	Voriconazole	VFEND	7
<b>Z</b>	Zafirlukast	Accolate	7

[a] Topical and vaginal metronidazole and miconazole are allowed.

— indicates no other name was available at the time this protocol was prepared.

## Listing 2

	Generic or Substance Name	Other Name (US Brand Name or Research Designation)	Minimum Washout Period (days)
<b>Opiate Agonist</b>			
<b>A</b>	Alfentanil	Alfenta	1
<b>C</b>	Codeine		1
<b>F</b>	Fentanyl	Fentora	7
<b>H</b>	Hydrocodone	Lorcet	1
	Hydromorphone	Dilaudid	1
<b>L</b>	Levorphanol	Levo-Dromoran	2

	<b>Generic or Substance Name</b>	<b>Other Name (US Brand Name or Research Designation)</b>	<b>Minimum Washout Period (days)</b>
<b>M</b>	Methadone	Dolophine	2
	Meperidine	Demerol	1
	Morphine	Duramorph	7
<b>O</b>	Oxycodone	Oxycontin	1
	Oxymorphone	Numorphan	1
<b>P</b>	Propoxyphene	Darvon	7
<b>S</b>	Sufentanil	Sufenta	1
<b>T</b>	Tramadol	Ultram	1
<b>Opiate Agonist-antagonist or Partial Agonists</b>			
<b>B</b>	Buprenorphine	Buprenex	1
	Butorphanol	Stadol	7
<b>N</b>	Nalbuphine	Nubain	1
<b>P</b>	Pentazocine	Talwin NX	1
<b>Other Sedating Medications or Substances</b>			
<b>B</b>	Buspirone	Ansial, Ansiced, Anxiron, Axoren, Bespar, BuSpar, Buspimen, Buspinol, Buspisal, Narol, Spitomin, Sorbon	7
<b>P</b>	Pimozide	Orap 15	15
	Propofol	Diprivan	7
<b>T</b>	Tetrahydrocannabinol	Marinol, Dronabinol, marijuana	7

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

This document cannot

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OPY  
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s thereof.

**Midazolam  
Injection, USP**



R<sub>x</sub> 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.

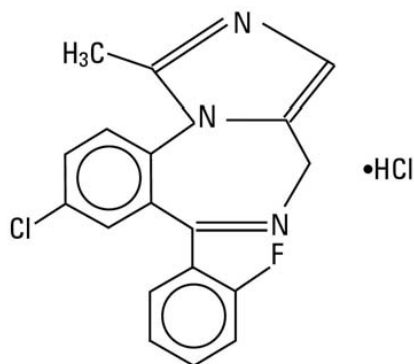
The initial intravenous dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system (CNS) 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 with [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<sub>18</sub>H<sub>13</sub>ClFN<sub>3</sub>•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 amnesic 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  $108 \pm 140$  seconds. This group was compared with pediatric patients who were given thiopental 5 mg/kg IV; 6 out of 6 closed their eyes at  $20 \pm 3.2$  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 ( $V_d$ ), 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 ( $V_d$ ) 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  $V_d$ . 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%)	<i>Local effects at IM Injection site</i>
	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:

hiccup(s) (3.9%)	<i>Local effects at the IV site</i>
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%, hiccup 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 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. 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 pre-sedation 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.

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## USUAL ADULT DOSE

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### INTRAMUSCULARLY

For preoperative sedation/anxiolysis/amnesia (induction of sleepiness or drowsiness and relief of apprehension and to impair memory of perioperative events).

For intramuscular use, midazolam should be injected deep in a large muscle mass.

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.

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)**

Responsiveness	Assessment Categories			Composite Score
	Speech	Facial Expression	Eyes	
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.

INTRAVENOUSLY BY  
INTERMITTENT INJECTION

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

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.

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.

- 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.
- 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.
- 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.
- 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

For sedation/anxiolysis/amnesia in critical care settings.

USUAL PEDIATRIC DOSE (NON-NEONATAL)

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

For sedation in critical care settings.

USUAL NEONATAL DOSE

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:**

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

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

<b>NDC No.</b>	<b>Container Description</b>	<b>Fill Volume</b>	<b>Total Midazolam (per container)</b>
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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EN-2248



## **Appendix 3 Amendment 4**

**Protocol Number: P261-401**

**Protocol Title:**

A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Intranasal Midazolam (USL261) in the Outpatient Treatment of Subjects with Seizure Clusters

ARTEMIS-1: Acute Rescue Therapy in Epilepsy with Midazolam Intranasal Spray-1

### **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 effects of USL261 on olfaction.

Change 2

The procedures to be completed at Visits 1, 4, and on the monthly telephone follow-up calls between Visit 3 and Visit 4 have been updated to add collection of the number of calls to EMS and ER visits for a seizure cluster or other seizure emergency prior to Visit 1 and during the study. This change has been made to allow for collection of number of calls to EMS and ER visits due to seizure emergencies prior to and during the study beyond use of EMS, ER, or the Rescue Protocol in the 24 hours after study drug administration. This will allow for assessment of healthcare utilization while USL261 is available to the caregiver and subject for the entire duration of the study.



Change 3

The introduction section was updated to reflect current study status.

Change 4

The time between Visit 2 (Test Dose) and Visit 3 (Randomization) was clarified. Visit 3 is to occur within 24 hours to 28 days of Visit 2. The time between Visit 2 and Visit 3 may be extended, the extension must be approved by the Sponsor or CRO designee.

**SECTIONS OF PROTOCOL AFFECTED BY CHANGE**

Change 1

**Synopsis – Safety Objective and 2.2 Safety Objective:**

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

**Synopsis – Safety Assessments:**

Collection of AEs, physical and neurological examinations, clinical laboratory evaluations, vital signs, caregiver-recorded respiration rate, 12-Lead ECG, pulse oximetry, sedation (determined by the OAA/S), C-SSRS, and the need for second dose of medication or emergency treatment, **and B-SIT**.

**Synopsis – Statistical Methods, Safety:**

- **Olfactory assessment results and changes from baseline will be presented by treatment group and visit.**

**Table 1 – Procedure Schedule:**

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

#### 6.1.2.1 Before Administration of Test Dose at Visit 2

- Administer B-SIT (see Section 6.2.2.9)

#### 6.1.4 Visit 3 (Randomization)

- Administer B-SIT (see Section 6.2.2.9)

#### 6.1.6 Visit 4 (Post Dose Assessment or Early Termination)

- Administer B-SIT (see Section 6.2.2.9)

#### 6.2.2.9 Brief Smell Identification Test

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 (pre-dose only), Visit 3, 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.

#### 10.5.4 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

**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					
<u>ER and EMS Visit Review [h]</u>	<u>X</u>				<u>X</u>

**[h] At Visit 1, collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency in the year prior to screening. At Visit 4, 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. Number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since last visit or follow-up phone call will also be collected on each monthly telephone follow up call between Visit 3 and Visit 4 or ET.**

### 6.1.1 Visit 1 (Screening Visit)

- **Collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency in the year prior to screening.**

### 6.1.6 Visit 4 (Post Dose Assessment or Early Termination)

- **Collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since Visit 3 or the most recent follow-up phone call.**

#### 6.1.6.1 Telephone Follow Up and Support

- **Collect number of calls to EMS and ER visits for a seizure cluster or other seizure emergency since Visit 3 or the most recent follow-up phone call.**

Change 3

## 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**

<u>Protocol No.</u>	<u>Objective(s) of the Study</u>	<u>Study Design and Type of Control</u>	<u>Test Product(s); Dosage regimen; Route of Administration</u>	<u>Number of Subjects; Age Range</u>	<u>Type of Subjects</u>	<u>Duration of Study</u>	<u>PD and Safety Assessments</u>
<i>Completed Studies</i>							
<u>MZ0714</u>	<u>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.</u>	<u>Open-Label, Five-Way Crossover, Randomized</u>	<u>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</u>	<u>25 Subjects 18 – 45 y</u>	<u>Healthy human volunteers</u>	<u>5 visits in approximately 5-6 weeks, preceded by a screen visit (-1 to -21 days)</u>	<u>SSS, DSST, OAA/S, physical exam, nasal exam, vital signs, TEAEs, oxygen saturation, subject sensory perception</u>
<u>MZ0815</u>	<u>Determine the safety, tolerability, PK and PD of ascending single- and two-dose regimens of USL261</u>	<u>Open-Label</u>	<u>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</u>	<u>An overall total of 90 subjects (60 adults 18-65 y; 30 adolescents 12-17 y)</u>	<u>Subjects with epilepsy taking stable doses of AEDs</u>	<u>4 visits for a total study duration of approximately 1 ½ to 6 weeks for each subject</u>	<u>SSS, DSST, OAA/S, physical (including nasal) and neurological exams, vital signs, TEAEs, oxygen saturation, subject sensory perception</u>
<u>P261-201</u>	<u>Evaluate the safety, tolerability, PK, and PD of ascending single- and two-dose regimens of USL261 compared with that of placebo</u>	<u>Randomized, Double-Blind, Placebo-Controlled, Dose Escalation</u>	<u>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</u>	<u>60 adult subjects; 18 – 65 y</u>	<u>Subjects with epilepsy taking stable doses of AEDs</u>	<u>4 visits (screening, 2 evaluation visits, and follow-up) over a 7 to 58 day time frame</u>	<u>TEAEs, vital signs, oxygen saturation; SSS, OAA/S, and Coding substest of Wechsler Adult Intelligence</u>

<u>Protocol No.</u>	<u>Objective(s) of the Study</u>	<u>Study Design and Type of Control</u>	<u>Test Product(s); Dosage regimen; Route of Administration</u>	<u>Number of Subjects; Age Range</u>	<u>Type of Subjects</u>	<u>Duration of Study</u>	<u>PD and Safety Assessments</u>
			<u>escalation occurred only after review of safety data.</u>				<u>Scale-IV (WAIS-IV)</u>
<u>P261-102</u>	<u>Evaluate the safety, tolerability, PK and PD of USL261 in geriatric and non-geriatric subjects</u>	<u>Randomized, Investigator and subject blind, Sponsor open</u>	<u>Subjects were randomized to receive a single dose of 2.5 and 5.0 mg USL261 at 2 study visits in a crossover fashion.</u>	<u>A total of 30 subjects (12 adult 18-40 y; 18 geriatrics ≥65 y)</u>	<u>Generally healthy geriatric and non-geriatric subjects.</u>	<u>4 visits (screening, 2 evaluation visits, and follow-up) over a 9 to 50 day time frame</u>	<u>TEAEs, vital signs, oxygen saturation; SSS, OAA/S, and DSST</u>
<u>Ongoing Studies</u>							
<u>P261-401</u>	<u>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)</u>	<u>Randomized, Double-Blind, Placebo-Controlled</u>	<u>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.</u>	<u>Planned: a maximum of approximately 240 subjects; ≥12y</u>	<u>Subjects with epilepsy who have seizure clusters</u>	<u>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</u>	<u>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</u>

<u>Protocol No.</u>	<u>Objective(s) of the Study</u>	<u>Study Design and Type of Control</u>	<u>Test Product(s); Dosage regimen; Route of Administration</u>	<u>Number of Subjects; Age Range</u>	<u>Type of Subjects</u>	<u>Duration of Study</u>	<u>PD and Safety Assessments</u>
<u>P261-301</u>	<u>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</u>	<u>Randomized, Double-Blind, Placebo-Controlled</u>	<u>Eligible subjects will be randomized 1:1 to receive 5.0 mg IN USL261 or placebo.</u>	<u>Planned: approximately 62 subjects; ≥12 y</u>	<u>Subjects with epilepsy admitted to the EMU who present seizure activity that meets defined Treatment Criteria</u>	<u>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</u>	<u>TEAEs, clinical laboratory evaluations, vital signs, ECGs (screening only), physical, nasal, and neurological exams, C-SSRS</u>

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.

~~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<sub>max</sub>) of midazolam was achieved in all dose groups within 10 minutes to 15 minutes post-administration. The C<sub>max</sub> 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%) was 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  $\geq 10\%$  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 suggests that they were related to route of administration.~~

~~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  $\geq 3$  days. USL261 was absorbed rapidly (approximately 13 to 20 minutes after a single dose; approximately 20 to 30 minutes after the 2-dose regimen) and the midazolam C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> general increased with total dose. Midazolam C<sub>max</sub> was lower in adolescents as compared to adults. The mean t<sub>1/2</sub> following the 2-dose regimen of USL261 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 antiepileptic drugs (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 adverse events AEs. Most TEAEs were mild to moderate in severity and deemed probably related to study drug. The most frequently reported TEAEs (reported by  $\geq 10\%$  of subjects) associated with the study drug were dysgeusia (86%), oropharyngeal pain (57%), rhinalgia (31%), and burning sensation (11%). One subject, who was administered a total dose of 12.5 mg USL261, 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.~~

~~USL has completed the clinical conduct of a third Phase I clinical trial (P261-201) entitled “A Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Study to Determine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intranasal Midazolam~~



~~(USL261) in Adult Subjects with Epilepsy on Stable Antiepileptic Drug Regimens". This 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  $\geq 3$  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.~~

~~USL has completed the clinical conduct of a fourth Phase I clinical trial (P261-102) entitled "A Randomized, Investigator and Subject Blind, Sponsor Open, Phase I Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intranasal Midazolam (USL261) in Healthy Geriatric and Non-Geriatric Subjects". This 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 ( $\geq 65$  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.~~

### 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<sub>max</sub>) of midazolam was achieved in all dose groups within 10 minutes to 15 minutes post-administration. The C<sub>max</sub> 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  $\geq 3$  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<sub>max</sub>, area under the plasma concentration time curve from time 0 to time of last measurable concentration (AUC<sub>0-t</sub>), and area under the plasma concentration time curve from time 0 extrapolated to infinity (AUC<sub>0-∞</sub>) generally increased with total dose. Midazolam C<sub>max</sub> was lower in adolescents as compared to adults. The mean t<sub>1/2</sub> 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  $\geq 10\%$  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<sub>max</sub> 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 (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.**

Change 4

### **3.4 Comparative Phase**

Subjects and caregivers will return to the study center for Visit 3 within 24 hours to 28 days of Visit 2 (unless DSMB review is not yet completed). **The time between Visit 2 and Visit 3 may be extended in certain cases; however, the extension must be approved by the Sponsor or CRO designee.**

#### **6.1.4 Visit 3 (Randomization)**

For subjects enrolled in the study after the initial DSMB review, Visit 3 will take place between 24 hours and 28 days after Visit 2. **The time between Visit 2 and Visit 3 may be extended in certain cases; however, the extension must be approved by the Sponsor or CRO designee.**

### Protocol Signature Page

**Authorized Sponsor Representative Signature:**

[Redacted Signature]

[Redacted Date]

[Redacted], Pharm.D.  
Upsher-Smith Laboratories, Inc.  
6701 Evenstad Drive  
Maple Grove, MN 55369-6026

Date

**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 Harmonisation E6, Guideline for Good Clinical Practice, and applicable regulatory requirements.

**Principal Investigator**

\_\_\_\_\_  
Name of Investigator (Print)

\_\_\_\_\_  
Site Number

\_\_\_\_\_  
Signature of Investigator

\_\_\_\_\_  
Date

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