Pharmacokinetics, pharmacodynamics, and safety of USL261, a midazolam formulation optimized for intranasal delivery, in a randomized study with healthy volunteers

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SUMMARY

Objective: To compare the pharmacokinetics, pharmacodynamics, and tolerability of USL261, a midazolam formulation optimized for intranasal delivery, versus midazolam intravenous (IV) solution administered intranasally (MDZ-inj IN) or intravenously (MDZ-inj IV) in healthy adults.

Methods: In this phase I, five-way crossover, open-label study, 25 healthy adults (aged 18–42 years) were randomly assigned to receive 2.5, 5.0, and 7.5 mg USL261; 2.5 mg MDZ-inj IV; and 5.0 mg MDZ-inj IN. Blood samples were collected for 12 h post dose to determine pharmacokinetic profiles. Pharmacodynamic assessments of sedation and psychomotor impairment also were conducted. Adverse events, oxygen saturation, and vital signs were recorded.

Results: Increasing USL261 dose corresponded with increases in midazolam area under the concentration time curve (AUC) and maximum observed plasma concentration (Cmax), with all doses demonstrating rapid median time to Cmax (Tmax; 10–12 min). USL261 also demonstrated increased absorption, with a 134% relative bioavailability, compared with the same MDZ-inj IN dose. USL261 was associated with dose-dependent increases in sedation and psychomotor impairment (p < 0.05); however, these effects lasted <4 h and generally did not differ from MDZ-inj IN or MDZ-inj IV at comparable doses. No serious adverse events (SAEs) or deaths were reported, and no treatment-emergent adverse events (TEAEs) led to study discontinuation.

Significance: Compared with intranasal delivery of a midazolam formulation intended for IV delivery, USL261, optimized for intranasal administration demonstrated improved bioavailability with similar pharmacodynamic effects. Therefore, USL261 may be a preferable alternative to the currently approved rectal diazepam treatment for intermittent bouts of increased seizure activity.

KEY WORDS: Seizure cluster, Acute repetitive seizure, Epilepsy, Rescue therapy.
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**KEY POINTS**

- USL261 demonstrated rapid time to peak midazolam concentration (10–12 min), and AUC and Cmax values increased with increasing doses from 2.5 to 7.5 mg
- Absolute and relative bioavailability were both higher with USL261 compared with MDZ-inj IN
- Psychomotor performance and sedation results were similar for all methods of midazolam administration, with return to near baseline values within 4 h
- Route of administration (IV vs. IN) may have the most influence on adverse events
- No serious adverse events were reported, and no participant was reported to have oxygen saturation below 90% or respiratory rate below 8 breaths/min

may be associated with increased mortality.3 The ideal out-of-hospital medication for SC/ARS would be highly effective, have rapid onset (minutes) along with a prolonged duration of action (hours), and be quick and easy to administer, with little or no monitoring required.4,5

Although it is widely accepted that benzodiazepines are the treatment of choice for rapid cessation of acute seizures, their usefulness may be hampered by the route of administration.4,5 In the hospital setting, intravenous (IV) benzodiazepines have a clearly established role; however, IV placement during a seizure requires skilled personnel, may be extremely difficult to accomplish, and could result in treatment delay. Because most seizures occur outside of hospitals, IV administration also is not always possible during a seizure emergency.

Given the limitations of IV delivery, alternative routes of seizure rescue medication administration have been explored. Currently, the only U.S. Food and Drug Administration (FDA)–approved rescue treatment for patients with intermittent bouts of increased seizure activity that can be administered by non–health care professionals is rectal diazepam gel (Diastat).6 Although Diastat has been used successfully in both home and hospital settings, it has drawbacks regarding its rectal dosing. There are concerns about the difficulty of administering rectal medication to a convulsing patient, and rectally administered drugs may be socially embarrassing,7–10 especially for older adolescents and adults. Despite these drawbacks, rectal diazepam is the only non-IV benzodiazepine currently marketed for this indication.

Midazolam is a potent anticonvulsant that has been used as a rescue therapy in seizure emergencies for >20 years.11–13 Its use in the United States for the treatment of seizures is not approved by the U.S. FDA, although buccal midazolam is approved in Europe for the treatment of prolonged, acute, convulsive seizures in patients aged 3 months to <18 years. A recent study titled Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) demonstrated that intramuscular (IM) delivery of midazolam provided significant advantage over IV lorazepam in the prehospital treatment of SE by paramedics.14 The number of patients without seizures by the time of arrival in the emergency department (ED) was superior with IM midazolam treatment, and significantly fewer subjects required ED admittance. The authors concluded that IM midazolam is the best currently available option for emergency medical services use in SE.

Intranasal (IN) administration of the midazolam IV formulation has been reported in the literature using a needleless syringe, either by dripping the solution into the nose7,8,10,15,16 or using a mucosal atomization device (MAD).9,17 However, the IV formulation has not been optimized for nasal delivery, a process that may require potential modifications to drug formulation, concentration, dosage, and/or dosing volume.18, 19 As cited by RAMPART authors, the relatively low concentrations of midazolam commercially available for atomized administration may be a limitation for intranasal use, although they state that RAMPART data are generally supportive of non-IV midazolam administration (e.g., IM, IN, buccal, and rectal).20

USL261, a single-dose nasal spray, is a formulation of midazolam optimized for nasal delivery, including an appropriate volume for this route of administration. USL261 is currently being developed as a rescue treatment for seizures in patients who require control of intermittent bouts of increased seizure activity (NCT01390220, NCT01529034, and NCT01999777). The objectives of the study presented here were to assess the pharmacokinetics and pharmacodynamic effects of a prototype formulation of USL261 in healthy adults, and to compare them with those of a midazolam intravenous solution delivered by IV and IN routes.

**METHODS**

**Study overview**

This phase 1 study was designed to assess the pharmacokinetics, pharmacodynamics, and safety profile of USL261 in healthy adults and compare these results with midazolam IV solution administered IN (MDZ-inj IN) and by IV infusion (MDZ-inj IV). The institutional review board (IRB) of the participating clinical site approved the study protocol, and participants provided written informed consent prior to conduct of study procedures.

**Study design**

Healthy adults (N = 25) were enrolled in a randomized, single-center, in-patient, open-label, five-way crossover study consisting of five dosing periods separated by a washout period of at least 3 days. For each study period, all participants were confined to the clinic the evening prior to dosing through approximately 12 h post-dosing.
Each participant was randomized to one of five different treatment sequences in which they received, in random order, USL261 (2.5, 5.0, 7.5 mg), MDZ-inj IV (2.5 mg), and MDZ-inj IN (5.0 mg). All doses of USL261 were administered by a single actuation in one nostril. For the MDZ-inj IV dose, midazolam IV solution (Hospira, Inc) was diluted to a final concentration of 2.5 mg in a total volume of 5 ml and infused IV over 15 min. The MDZ-inj IN dose administered a total of 1 ml of undiluted midazolam IV solution (5 mg/ml) by dripping half the dose in each nostril in a slow stream over 15 s via a needleless syringe.

Participants

Healthy adults (aged 18–45 years) within 25% of ideal body weight were eligible for inclusion in the study population. Participants with acute or chronic nasal symptoms, nasal polyps, deviated septum, or other physical abnormalities of the nose were excluded. Participants with a current diagnosis of sleep apnea, heart failure, cardiac conduction defect, chronic respiratory disease, depressive disorder, or psychosis were also excluded. Any participant who received drugs, vaccines, or supplements that could affect midazolam metabolism or nasal physiology within 7 days prior to study drug administration was not eligible to enroll in the trial. Participants were also excluded if they had a history of regular use of sedative/hypnotic medication or use of any sedative/hypnotic medications within 2 weeks of study drug administration.

Pharmacokinetic measures

Blood samples were collected for pharmacokinetic assessments at predose, and 5, 10, 15, 20, 30, 45, 60, 90 min and 2, 3, 4, 6, 12 h postdose. Plasma concentrations of midazolam and its major metabolite, α-hydroxymidazolam (1-OH MDZ), were determined by reverse-phase high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) using the Sciex API3000 or API4000. The lower limit of quantification with this method was 0.5 ng/ml. The assay was linear for midazolam and 1-OH MDZ from 0.5 to 256 ng/ml and has been validated for use on human samples obtained during clinical studies. The coefficient of variation (CV) for this assay at 0.5 ng/ml was 9.0% for midazolam and 8.7% for 1-OH MDZ; at 256 mg/ml, CV was 4.5% and 2.7%.

Pharmacodynamic evaluations

Psychomotor impairment was assessed using the Digit-Symbol Substitution Test (DSST),21 which measures associative ability and performance based on a digit symbol code where each of nine digits is paired with a different symbol. Outcome of the DSST is based on the number of symbols corresponding to each digit completed in 90 s. DSST assessments were performed at predose, and 10, 20, 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 12 h postdose.

Sedation was assessed using two validated instruments: the Stanford Sleepiness Scale (SSS)22 and the Observer’s Assessment of Alertness/Sedation Scale (OAA/S).23 The SSS is a self-reported assessment that evaluates sedation on a scale from one to seven, with higher values signifying increasing levels of sedation. The OAA/S is a clinician-rated qualitative categorical measure of sedation, with lower scores signifying increasing levels of sedation. Participants were evaluated in each of the four OAA/S categories: responsiveness, speech, facial expression, and eyes. The OAA/S composite score was defined as the lowest score in any one of the four assessment categories. Both assessments of sedation were performed at predose, and 5, 10, 15, 30, 45, 60, 75, 90, 105 min and 2, 3, 4, 6, 8, 12 h postdose.

Safety and tolerability assessments

Safety and tolerability assessments were conducted throughout the study. Spontaneously reported treatment-emergent adverse events (TEAEs) were classified by study investigator based on intensity (mild, moderate, or severe) and relationship to study drug (not related, possibly related, probably related, or definitely related). Vital signs including heart rate and blood pressure were monitored. Pulse oximetry and respiratory rate were also measured; oxygen saturation of <90% for >30 s was recorded as a TEAE.

Study populations and statistical analyses

Demographics, baseline characteristics, and safety/tolerability analyses were based on the safety population, defined as all randomized participants who received at least one dose of study drug. The pharmacokinetic and pharmacodynamic populations were defined as all participants who completed all five treatment periods and had sufficient plasma samples for accurate estimation of pharmacokinetic parameters.

Pharmacokinetic analyses

All pharmacokinetic analyses were performed on the defined pharmacokinetic population unless otherwise stated. Midazolam pharmacokinetic parameters were calculated using noncompartmental methods24,25 (WinNonlin Professional, version 5.2; Pharsight Corporation, Cary, NC, U.S.A.) and included area under the plasma concentration–time curve from time zero to the last measurable time point (AUC_0–t) and time zero to infinity (AUC_0–∞), terminal elimination half-life (t_1/2), peak midazolam plasma concentrations (C_max.), and the time to C_max (T_max). Both absolute (ratio of AUC_0–∞ for USL261 or MDZ-inj IN to MDZ-inj IV) and relative (ratio of AUC_0–∞ for USL261 to MDZ-inj IN) bioavailability were also determined, with the comparator value set at 100%. Only AUC and C_max were calculated for the 1-OH MDZ metabolite.

To evaluate equivalence between USL261 5.0 mg and MDZ-inj IN 5.0 mg, an analysis of variance (ANOVA) with fixed effects (sequence, treatment, and period) and random
effects (participant nested within sequence) was performed on log-transformed AUC and C_{max} data to obtain geometric least-squares mean (GLSM) for each treatment group. The ratio of GLSM between the USL261 5.0 mg and MDZ-inj IN 5.0 mg treatment groups were calculated. If the 90% confidence interval (CI) of the GLSM ratio was completely contained within the 0.8–1.25 equivalence range, USL261 5.0 mg and MDZ-inj IN 5.0 mg were to be considered pharmacokinetically equivalent.

Pharmacodynamic analyses

Mean changes from baseline for each of the time points of the pharmacodynamic assessments (DSST, SSS, and OAA/S) were calculated for all treatments. For the DSST, change from baseline trial completion rate (calculated as number of trials attempted/90 s) was also evaluated. Peak effects and time to peak effects of the pharmacodynamic assessments were analyzed using an ANOVA model, with fixed effects for sequence, treatment, and period, and with a random effect for participant nested within sequence. Pairwise comparisons between treatment groups were performed (α = 0.05) on least-squares (LS) means, with standard error.

Pharmacodynamic data from single-data points that were missing for administrative reasons were not imputed and were excluded from analysis; no participants were excluded from the analyses. If components of the OAA/S score were missing, the lowest score among those available was used when calculating the composite score. If pharmacodynamic data were missing due to participants falling asleep, analyses were performed using the observed values. For the SSS, if a participant was unable to respond due to being asleep, a score of seven (participant no longer fighting sleep, sleep onset soon; having dream-like thoughts) was used for analyses.

Results

Patient disposition and demographics

A total of 25 healthy adults were randomized to one of five treatment sequences. The mean (standard deviation, SD) age of the study population was 30 (6.7) years (range 18–42 years). The majority of participants were male (60%) and white (68%), with an additional 28% black and 4% other (n = 1 self-identified as black/white). The mean (SD) weight of the participants was 77.1 (13.4) kg. All 25 participants completed the five treatment periods and were included in the pharmacokinetic, pharmacodynamic, and safety populations.

Pharmacokinetic profiles

Midazolam

The mean plasma concentration–time curves for all five treatments are presented in Figure 1, with the inset providing details of the first 60 min postdose. USL261 demonstrated rapid time to peak midazolam concentration (median T_{max} 10–12 min), and the IV midazolam solution given either IN or IV had a median T_{max} of 15 min (Fig. 1, Table 1), although it should be noted that MDZ-inj IV was infused over 15 min. The mean half-life for all treatments was similar and ranged from 3.6 to 4.0 h (Table 1).

α-Hydroxymidazolam

As with the parent midazolam compound, increasing doses of USL261 corresponded with increases in the AUC_{0–∞} and C_{max} of 1-OH MDZ levels (Table 1).

Bioavailability and pharmacokinetic equivalence

The absolute bioavailability of USL261 for all administered doses was greater than MDZ-inj IN (62–73% vs. 50%, respectively), which results in increased relative bioavailability of USL261 versus MDZ-inj IN (125–149%; Table 2). When directly compared, the same dose (5.0 mg) of USL261 and MDZ-inj IN were not equivalent, as the confidence intervals for the AUC_{0–∞} and C_{max} ratios, 1.31 (1.18–1.44) and 1.33 (1.15–1.53), respectively, were greater than the 0.8–1.25 equivalence values.

Pharmacodynamics effects – psychomotor performance

In the assessment of psychomotor performance using the DSST, greater impairment of psychomotor performance was observed with increasing doses of USL261 (Fig. 2). For all IN dosing groups, the mean maximal effect on DSST occurred 10–20 min after study drug administration; mean maximal effect for MDZ-inj IV 2.5 mg was observed at the end of infusion (15 min). Dose-dependent increases in
maximal impairment of psychomotor performance by USL261 were significant \(p < 0.001\). As expected, the greatest mean reduction from baseline in the rate of trial completion on the DSST (trials attempted/s) was observed in participants receiving the highest midazolam dose (USL261 7.5 mg). At a comparable dose, maximal impairment was significantly greater with MDZ-inj IV 2.5 mg than USL261 2.5 mg \(p = 0.004\); however, maximal impairment was not significantly different between USL261 5.0 mg and MDZ-inj IN 5.0 mg. Mean DSST values for most participants returned to near baseline by 4 h for all treatment groups (Fig. 2).

### Pharmacodynamic effects – sedation

Using the SSS, participants reported maximal sedation effects of USL261 and MDZ-inj IN between 45 and 60 min postdose (Fig. 3A); clinician-rated OAA/S scores indicated maximal effects between 30 and 75 min postdose (Fig. 3B). Maximal sedation effect for MDZ-inj IV was observed at the end of the 15 min infusion on both the SSS and OAA/S. With IN delivery, maximal sedation times were recorded after \(T_{\text{max}}\) (the 10–15 min required to reach \(C_{\text{max}}\)). No significant differences in peak sedation effects were observed between USL261 2.5 mg and MDZ-inj IV 2.5 mg, or between USL261 5.0 mg and MDZ-inj IN 5.0 mg, on either the SSS or OAA/S. Similar to results for psychomotor impairment, mean sedation scores for the SSS and OAA/S returned to near baseline 4 h postdose with all treatments.

### Table 1. Pharmacokinetics of midazolam formulations \((N = 25)\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>USL261</th>
<th>MDZ-inj IV(^a)</th>
<th>MDZ-inj IN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>2.5 mg 5.0 mg 7.5 mg</td>
<td>2.5 mg 5.0 mg</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AUC_{0-\infty}), mean (SD), ng·h/ml</td>
<td>93 (26) 170 (54) 238 (78)</td>
<td>142 (63) 128 (32)</td>
<td></td>
</tr>
<tr>
<td>(C_{\text{max}}), mean (SD), ng/ml</td>
<td>59 (18) 73 (20) 93 (28)</td>
<td>119 (71) 55 (14)</td>
<td></td>
</tr>
<tr>
<td>(T_{\text{max}}), median (range), min</td>
<td>10 (5–30) 10 (5–30) 12 (5–45)</td>
<td>15 (5–46) 15 (5–60)</td>
<td></td>
</tr>
<tr>
<td>(t_{1/2}), mean (SD), h</td>
<td>3.6 (0.8) 3.8 (1.0) 3.6 (0.9)</td>
<td>4.0 (1.6) 3.6 (0.7)</td>
<td></td>
</tr>
<tr>
<td>(\alpha)-Hydroxymidazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AUC_{0-\infty}), mean (SD), ng·h/ml</td>
<td>13 (4.6) 29 (9.6) 44 (13)</td>
<td>14 (4.7) 27 (8.9)</td>
<td></td>
</tr>
<tr>
<td>(C_{\text{max}}), mean (SD), ng/ml</td>
<td>4.2 (2.0) 8.9 (5.2) 13 (7.8)</td>
<td>3.9 (1.7) 11 (7.1)</td>
<td></td>
</tr>
</tbody>
</table>

\(AUC_{0-\infty}\), area under the concentration time curve from time 0 to infinity; \(C_{\text{max}}\), maximum observed plasma concentration; IN, intranasal; IV, intravenous; MDZ-inj, midazolam IV solution (given IV or IN); SD, standard deviation; \(T_{\text{max}}\), time to maximum observed plasma concentration; \(t_{1/2}\), terminal elimination half-life.

### Table 2. Bioavailability of midazolam formulations \((N = 25)\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>USL261</th>
<th>MDZ-inj IV(^a)</th>
<th>MDZ-inj IN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>2.5 mg 5.0 mg 7.5 mg</td>
<td>2.5 mg 5.0 mg</td>
<td></td>
</tr>
<tr>
<td>Absolute bioavailability, %(^b)</td>
<td>73(^c) 65(^c) 62(^c)</td>
<td>100(^d) 50(^d)</td>
<td></td>
</tr>
<tr>
<td>Relative bioavailability, %(^d)</td>
<td>149(^c) 134(^c) 125(^c)</td>
<td>– 100(^d)</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{IN}, \text{in intranasal; IV, intravenous; MDZ-inj, midazolam IV solution (given IV or IN).}\)

\(^{a}\)15-min infusion.

\(^{b}\)Ratio of \(AUC_{0-\infty}\) of USL261 or MDZ-inj IN to MDZ-inj IV.

\(^{c}\)Dose-adjusted value.

\(^{d}\)Reference value was set at 100% for calculations.

\(^{e}\)Ratio of \(AUC_{0-\infty}\) of USL261 to MDZ-inj IN.

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**Figure 2.**

Mean change from baseline in Digit-Symbol Substitution Test (DSST) completion rate for all formulations and delivery routes. Lower scores indicate greater psychomotor impairment. Solid lines with closed symbols indicate USL261 and dashed lines with open symbols MDZ-inj. Squares indicate 2.5 mg dose, circles 5.0 mg dose, and diamond 7.5 mg dose. Inset is a detail of the first 60 min postdose.

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Dose-dependent sedation

Dose-dependent increases in maximal sedation effect were observed on the SSS with USL261 administration (2.5 vs. 5.0 mg, p = 0.024; 2.5 vs. 7.5 mg, p < 0.001). When evaluated on the OAA/S, the only significant increase in peak sedation effect was found between the lowest and highest doses of USL261 (2.5 vs. 7.5 mg, p = 0.002). In all treatment groups, on both rating scales, highest sedative effects were reported with the 7.5 mg dose of USL261.

Oversedation, defined as a composite OAA/S score of one, occurred in one participant at two different doses of USL261 (5.0 mg, 7.5 mg). A score of one was reported for this participant at 30-, 45-, 60-, and 75-min postdose (5.0 mg) and only at 45 min after the 7.5 mg dose. The participant recovered to predose alertness approximately 4–6 h after both doses of USL261, with no need for resuscitative intervention.

Safety and tolerability

All 25 participants reported at least one TEAE during the study, and a total of 208 TEAEs were reported. All TEAEs were considered mild, with most (95.7%) considered probably related to study drug. Overall, the most common drug-related TEAEs were nasal discomfort (84%), throat irritation (84%), increased lacrimation (76%), and dysgeusia (72%). Based on the verbatim term and TEAE onset/duration, the preferred term “dysgeusia” likely represents complaints about the taste of study medication as opposed to alteration in taste. TEAEs reported in at least two participants in any treatment group are presented in descending order of occurrence in Table 3. The incidence of TEAEs was similar across all IN treatment groups, and did not increase with increasing doses of USL261. There were no reports of a TEAE with MDZ-inj IV (Table 3). No serious adverse events (SAEs) or deaths were reported, and no TEAEs led to study discontinuation.

Respiratory and cardiovascular effects

No respiratory or cardiovascular effects were deemed adverse events; vital sign values of note are detailed below. No participant was reported to have oxygen saturation below 90% or respiratory rate (RR) below 8 breaths/min, although postdose RR of eight or nine breaths/min was recorded in six participants (all treatment groups except USL261 7.5 mg). One participant had heart rate measurements <50 beats/min (BPM) that were >2 BPM change from predose during the MDZ-inj IN 5.0 and USL261 2.5 mg treatment periods; decreases from predose baseline heart rate were 19 and 9 BPM, respectively. Heart rates above 110 BPM were experienced by two participants on one or more occasions during the study; change from predose baseline was 29 BPM for one participant (MDZ-inj IV 2.5) and up to 31 beats/min for the other (USL261 5.0 mg and 7.5 mg). In all treatment groups, mean systolic and diastolic blood pressure decreased slightly; however, decreases in blood pressure did not appear to be dose related and returned to baseline levels within 4–8 h.

Discussion

The results from this phase 1 study confirm that midazolam is quickly and consistently absorbed following IN dosing, with either USL261 or MDZ-inj IN use; however, both absolute and relative bioavailability of midazolam were higher with USL261 compared with MDZ-inj IN. When adjusted for dose, USL261 had an average of 36% higher relative bioavailability than MDZ-inj IN. Both systemic exposure (AUC) and peak plasma concentrations (Cmax) increased with increasing doses of USL261. In addition, the terminal elimination half-life (t1/2) of USL261 was not significantly different compared with any of the other treatment groups.
Although no formulation of midazolam is currently approved for intranasal delivery, pharmacokinetic results for USL261 5.0 mg were within ranges previously reported in studies evaluating ~5.0 mg midazolam administered IN (100–300 μl doses) in healthy participants. Systemic and peak plasma concentrations for IN midazolam ranged from 134 to 198 ng·h/ml26–29 (170 for USL261) and 42–84 ng/ml26–31 (73 for USL261), respectively. Time to peak plasma concentration and half-life was also similar for USL261 5.0 mg (12 min and 3.8 h, respectively) compared with 1.3–1.5 h, respectively).26–31

Finally, absolute bioavailability of USL261 5.0 mg (65%) was within values previously reported for IN midazolam (61–83%).26–31

As pharmacokinetics (PK) and efficacy outcomes can potentially be affected by large IN dosing volumes, the PK studies above were limited to those administering small volumes of midazolam tailored for IN delivery via atomizers in order to make relevant comparisons. In contrast, other PK and efficacy studies evaluate midazolam by dripping the IV solution directly in the nose.7,8,10,15,16,32,33 Use of IV midazolam administered IN may be problematic for multiple reasons, including the large dosing volume required and the lack of physiochemical modification of midazolam for nasal delivery, which may lead to reduced reliability during administration (e.g., decreased nasal absorption, swallowing excess drug volume). This reduced reliability in drug administration is supported by data from our study, where USL261—optimized with an appropriate volume for nasal delivery and improved ease of use—had a higher relative bioavailability and faster median Tmax compared with MDZ-inj IN.

Table 3. Incidence of TEAEs occurring in ≥2 participants in any treatment group (N = 25)

<table>
<thead>
<tr>
<th>Drug Dose</th>
<th>USL261 2.5 mg</th>
<th>USL261 5.0 mg</th>
<th>USL261 7.5 mg</th>
<th>MDZ-inj IV 2.5 mg</th>
<th>MDZ-inj IN 5.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with ≥1 TEAE, n (%)</td>
<td>19 (76)</td>
<td>17 (68)</td>
<td>17 (68)</td>
<td>0</td>
<td>22 (88)</td>
</tr>
<tr>
<td>TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Throat irritation</td>
<td>14 (56)</td>
<td>12 (48)</td>
<td>14 (56)</td>
<td>0</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>11 (44)</td>
<td>8 (32)</td>
<td>12 (48)</td>
<td>0</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>9 (36)</td>
<td>9 (36)</td>
<td>7 (28)</td>
<td>0</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>8 (32)</td>
<td>5 (20)</td>
<td>8 (32)</td>
<td>0</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

IN, intranasal; IV, intravenous; MDZ-inj, midazolam IV solution (given IV or IN); TEAE, treatment-emergent adverse event.

Although midazolam has been shown to lead to significantly reduced time to seizure cessation versus IV diazepam in the ED,34 and the RAMPART authors speculated that an earlier time to administration of IM midazolam may also have led to improved outcomes versus IV lorazepam.14

In this study, psychomotor performance (DSST) and sedation (SSS and OAA/S) results were similar with all methods of midazolam administration (IN and IV), and return to near baseline values was seen within 4 h. This return to baseline is similar to other pharmacodynamic assessments with midazolam administered IN25 and rectal diazepam,35 although diazepam was not investigated in this study. The effect of midazolam on psychomotor performance and sedation was dose dependent in this study, which also is consistent with pharmacodynamic findings in studies of other intranasal midazolam formulations.26,28,36 Peak effect on psychomotor performance with DSST was seen 10–20 min after IN administration, which is similar to the time to peak effect (13–18 min) seen in electroencephalography (EEG)–measured pharmacodynamic parameters after midazolam treatment.37 On the patient-reported measure of sedation (SSS), peak effect was reported 45–65 min after drug administration; on the clinician-rated scale (OAA/S), peak effect was reported 30–75 min postdose. When using any drug with the potential for sedative effects, it should be noted that even patients who do not report sedation may still be impaired when performing activities of daily living.

In this single-dose study, no serious safety concerns were identified. The most common drug-related TEAEs (nasal discomfort, throat irritation, increased lacrimation, and dysgeusia) were observed only in the dose groups where midazolam was administered via the IN route, independent of dose, which suggests that they may be related to route of administration.

One limitation is that the study was conducted in healthy volunteers with no evidence of any nasal obstruction, infection, or inflammatory condition. In addition, because these assessments were not performed in patients requiring rescue treatment, the possible effects of seizures on the delivery of USL261 and subsequent pharmacodynamic responses were

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not evaluated. Studies of USL261 in patients with epilepsy are currently ongoing.

As described in the introduction, rectal diazepam is the only approved at-home seizure rescue treatment. Although the goal of this clinical pharmacology study was limited to pharmacokinetic and pharmacodynamic analyses in healthy participants, previous comparative studies evaluating the efficacy of different midazolam formulations administered IN versus rectal diazepam in children and adults with epilepsy found that midazolam administered IN was as effective as9,38 or significantly more effective than rectal diazepam in pediatric patients with epilepsy.9 Holsti et al. reported similar results and suggested that IN midazolam is at least as effective as rectal diazepam.38 In addition, patients treated with rectal midazolam showed a significantly higher incidence of side effects (13, 16%) compared with the IN route (0%).18 These differences may be due to differences in the pharmacodynamic effect of the two formulations or could be due to the inherently different routes of administration.

Together with this historical perspective of midazolam administered intranasally, these results support the continued development of this novel prototype formulation of midazolam nasal spray (USL261) that may provide an important non-IV alternative to the currently available treatment options for intermittent bouts of increased seizure activity.

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CONFLICTS OF INTEREST

Dr. Barry Gidal has received support from, and served as a paid consultant for, Upsher-Smith Laboratories, Inc. In addition, within the last 3 years, he received speakers or consultancy support from GlaxoSmithKline, UCB, Eisai Inc., and Sunovian Pharmaceuticals Inc. Dr. Keith Rodvold served as a paid pharmacokinetic consultant for StatWorks Inc. for the data analysis of this study. In addition, within the past 3 years, he received speakers or consultancy support from Achaogen, Cubist Pharmaceuticals (including Trius Therapeutics), Durata Therapeutics, Forest Laboratories, GlaxoSmithKline, Pfizer Inc., Remepx Pharmaceuticals, and Theravance Inc. Drs. Bancke, Dvorak, and Halverson are employees of Upsher-Smith Laboratories, Inc. We, the authors, confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES


