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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Emily R. Freilich, MD
NDA 211321 Nayzilam (Intranasal midazolam)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	211321
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Division/Office	Division Neurology Products/ODE I/Office of New Drugs
Reviewer Name(s)	Emily R. Freilich, M.D.
Review Completion Date	02/20/2019
Established/Proper Name	Midazolam
(Proposed) Trade Name	Nayzilam
Applicant	Proximagen
Dosage Form(s)	Single use drug-device product for nasal inhalation (5mg/0.1ml)
Applicant Proposed Dosing Regimen(s)	5 mg intranasally (IN), may be repeated x 1 after 10 minutes
Applicant Proposed Indication(s)/Population(s)	Patients age 12 years and older with acute repetitive seizures, seizure clusters, (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	NAYZILAM is a benzodiazepine indicated for acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older.

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
AED	antiepileptic drug
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPR	cardiopulmonary resuscitation
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DSMB	data and safety monitoring board
DZP	diazepam
ECG	electrocardiogram
eCTD	electronic common technical document
EMS	emergency medical services
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
IAMC	Interim Analysis Monitoring Committee
IRT	Interactive Response Technology System
ICH	International Council for Harmonization
IN	intranasal
IV	intravenous

IM	intramuscular
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LZP	lorazepam
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MDZ	midazolam
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMP	patient management plan
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TSQM	treatment satisfaction questionnaire for medication
USL	Upshur Smith Laboratories, INC
VNS	Vagus Nerve Stimulator

1. Executive Summary

1.1. Product Introduction

Nayzilam is an intranasal (IN) combination drug-device product intended for the acute treatment of seizures in patients 12 years of age and older who require control of intermittent episodes of increased seizure activity (i.e., seizure clusters, acute repetitive seizures). Midazolam (MDZ), the active ingredient, is a short-acting benzodiazepine, initially approved in the United States (US) for sedation in 1985 under the trade name Versed (NDA 018654). It is currently marketed as a generic drug in the US in intravenous (IV), intramuscular (IM), and oral formulations for adults and children for sedation/anxiolysis/and amnesia, induction of anesthesia prior to administration of other anesthetic agents, and for sedation of intubated and mechanically ventilated patients. Most recently, Seizalam, an intramuscular injection formulation of MDZ, was approved (September 2018) for the emergency treatment of status epilepticus in adult patients. This approval was the first approval in the US for MDZ use in the treatment of seizures. There is also a buccal form of MDZ that is marketed in Europe and many countries around the world for the treatment of prolonged seizures in children.

This application is a 505(b)(2) application, and includes a new dosage form, new combination product, new indication, and new route of administration (intranasal). The applicant proposes treatment with a 5 mg single-use vial, administered as one intranasal spray, with the allowance of a repeat dose after 10 minutes when needed, and a limit of 2 doses (b) (4). The product will most likely be utilized on chronic, intermittent basis, as it will likely be given as needed for each seizure cluster or episode of acute repetitive seizures. The delivery device is packaged as a single-use vial with aspirator, and comes in a package of 2 vials.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Evidence of effectiveness for Nayzilam when administered via nasal inhalation from a single use vial is based on the robust, positive results of the single multicenter pivotal trial.

The level of evidence provided is adequate to support the conclusion that intranasal midazolam is effective for the treatment of acute repetitive seizures.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Nayzilam is an intranasal preparation of midazolam. Intravenous or Intramuscular midazolam is already approved for sedation and anesthesia, and more recently, for the treatment of status epilepticus. Midazolam has a long history of off-label treatment for various seizure types, including status epilepticus, seizure clusters, and acute repetitive seizures. Nayzilam is packaged as a single dose unit vial, and is administered as a single, one-time intranasal spray (administering 5 mg midazolam per spray).

Nayzilam is proposed for the acute treatment of patients with seizure clusters. Seizure clusters (also called acute repetitive seizures) occur in a small subset of patients with epilepsy and are typically defined as intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern. Seizure clusters may progress, untreated, to status epilepticus, a life-threatening emergency. Therefore, many patients with seizure clusters require a rescue plan for treatment of their clusters to prevent progression to prolonged seizures. The only approved treatment for seizure clusters is rectal diazepam, which may work well in young children, but is progressively more difficult to administer as patients get older. It is not always practical or convenient to use rectal diazepam, especially in seizure clusters where a patient may be awake and alert in between their brief seizures. Occasionally other benzodiazepines are prescribed off-label for the treatment of seizure clusters, but these drugs lack established efficacy and their use may also result in inaccurate dosing, or intranasal, buccal, or rectal administration of formulations intended for injection.

The efficacy of Nayzilam was demonstrated in a single, randomized, double-blind, clinical trial. The placebo-controlled trial was conducted in epilepsy patients age 12 years and older, with a history of documented, recognizable, seizure clusters. All enrolled patients were initially given an in-clinic test dose, with monitoring of vital signs and laboratory tests, and then they were randomized to either Nayzilam 5 mg or placebo to be given by a caregiver, in an outpatient setting, at the time of their next seizure cluster. An optional, open-label, second 5 mg dose was used for patients who did not respond to the first dose. Treatment success was defined as termination of seizures within 10 minutes and no recurrence of seizures within 6 hours. The proportion of patients who were a treatment success was significantly higher in the Nayzilam group (53.7%) compared to the placebo group (34.3%). Similar benefits were seen on key secondary endpoints of time to next seizures and recurrence of seizures within 24 hours.

Given the class effect of the use of benzodiazepines in the treatment of seizures of multiple types, the Agency previously determined that a single, robust, and adequate clinical trial might be sufficient for demonstration of effectiveness.

Benzodiazepines also have a well-characterized safety profile. Midazolam is known to cause sedation and respiratory depression, especially in the setting of certain concomitant medications or pre-existing respiratory disease. The safety profile of Nayzilam in the clinical trials was

acceptable, with evidence of somnolence which resolved within 4 hours, and transient adverse events from administration, including nasal discomfort, throat irritation, and increased eye lacrimation. These effects were transient and resolved within 30 minutes. Although data were limited, there was no evidence of nasal mucosa toxicity or olfactory toxicity. In general, the literature supports lack of nasal mucosa toxicity with potentially more irritating forms of intranasal midazolam.

There was no clinically significant respiratory depression seen in the outpatient treatment of seizure clusters, and only a few mild events in the test-dose phase that resulted in discontinuation. Proper training for caregivers on administration and monitoring for when to seek further care can alleviate the majority of the risks. Because of the risk of tachyphylaxis associated with chronic use of benzodiazepines, treatment frequency should not exceed every 3 days or more than 5 times per month.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Seizure clusters are intermittent, recurrent, stereotyped, and recognizable episodes of increased seizure activity that differ from non-cluster seizure activity. Clusters occur in a small subset of patients with epilepsy. Seizure clusters may lead to life-threatening episodes of prolonged seizures and/or status epilepticus. Seizure clusters require frequent trips to the emergency room (ER) for seizure stabilization. Patients often require a “rescue treatment” for their seizure clusters. 	There is an unmet medical need for the treatment of seizure clusters and other episodic, recurrent bouts of increased seizure activity. If treated promptly, there would significant reduction in use of emergency medical services (EMS)/ER resources, and reduction in the risk of more severe complications (e.g., progression to status epilepticus).
Current Treatment Options	<ul style="list-style-type: none"> The only FDA-approved treatment is rectal diazepam, which is approved for the management of patients with epilepsy who require intermittent use of diazepam to control bouts of increased seizure activity. 	The only currently approved treatment alternative is rectal diazepam which is not practical for patients over a certain age because of the size of the patients, difficulty

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> Rectal diazepam has many drawbacks including difficulties with administration, social stigma, and patient compliance. Off-label benzodiazepines are often prescribed for rescue treatment for seizure clusters. Parenteral midazolam currently given intranasally through a syringe has potential risks of misuse, inaccurate dosing, or local toxicity from the low pH. 	with administration, or social stigma. These problems often result in poor compliance with rescue treatment plans. Off-label use of benzodiazepines may be prescribed, but the use of parenteral medications intranasally or buccally can lead to dosing errors.
Benefit	<ul style="list-style-type: none"> In a single, adequate, and well-controlled pivotal study, Nayzilam demonstrated effectiveness compared to placebo in the proportion of patients who met the definition for treatment success: which included termination of seizures within 10 minutes and no seizure recurrence for 6 hours after dose (53.7% versus 34.3%; $p = 0.0069$). Nayzilam demonstrated longer time to next seizure after study drug administration compared to placebo. Nayzilam had lower incidence of seizure recurrence in 24 hours following study drug administration compared to placebo. Nayzilam's route of administration has benefits over rectal diazepam in terms of ease of use, and caregiver and patient preference. Benzodiazepines, as a class, have previously demonstrated benefit in the treatment of various seizure types and epilepsies, including status epilepticus, that indicates a class effect. 	<p>Nayzilam 5 mg single dose nasal spray was found to be effective in the treatment of seizure clusters, resulting in termination of seizures and prevention of seizure recurrence for 6 hours, with some benefit lasting up to 24 hours.</p> <p>The benefit in patients with seizure clusters is clinically and statistically significant, and the intranasal route of administration has significant benefits as well.</p> <p>Thus, the robust findings of a single study are deemed sufficient for evidence of effectiveness given the class antiepileptic effectiveness of benzodiazepines.</p>
Risk and Risk Management	<ul style="list-style-type: none"> Nayzilam appears to be well-tolerated in patients age ≥ 12 years of age. The safety profile of benzodiazepines is well-characterized, with risks including sedation and respiratory depression. There were no concerning new safety signals for intranasal midazolam. 	Nayzilam appears to be well-tolerated, with no major safety signals and no clear evidence of nasal or mucosal toxicity. The adverse event profile of Nayzilam is acceptable, and consistent with known adverse reactions for benzodiazepines. Somnolence was common,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • Respiratory depression was not seen when Nayzilam was administered in the outpatient setting for treatment of seizure clusters. • The most common treatment-emergent adverse events (TEAEs) include somnolence and route of administration adverse events (AEs) such as nasal discomfort, throat irritation, and eye lacrimation. • The route of administration AEs are transient and mostly resolved within 30 minutes of administration. • The somnolence tends to be transient and patients are mostly awake within 4 hours and back to functional baseline within 24 hours. • The published literature does not demonstrate any evidence of nasal mucosal toxicity or olfactory toxicity, despite use of a potentially more irritating formulation of intranasal midazolam. • The device is easily actuated and may waste the dose if caregiver does not have proper training prior to administration. • There are associated risks with chronic use and dependence, as well as potential withdrawal symptoms from chronic daily use of benzodiazepines. • Drug-drug interactions with moderate and strong CYP3A4 inhibitors can significantly reduce MDZ clearance, and result in higher exposures and more pronounced central nervous system depressant effects. 	<p>but respiratory depression does not appear to be a concern at the proposed dosage and indication.</p> <p>Use in the outpatient, community setting will require proper patient and caregiver training for instructions on when to use, how to administer, and a rescue plan for when to seek further care.</p> <p>Concomitant use with strong CYP3A4 inhibitors should be contraindicated. A warning should state that use with concomitant moderate inhibitors of CYP3A4 is not recommended unless benefits outweigh risks.</p> <p>A test dose, while not required, should be considered for high-risk patients. The treatment should be given no more than every 3 days and no more than 5 times monthly, the treatment frequency studied treatment in the open-label long-term safety study.</p>

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	X Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	X Patient reported outcome (PRO)	Sec 6.1, 6.2 Study Endpoints
	X Observer reported outcome (ObsRO)	Sec 6.1, 6.2 Study Endpoints

2. Therapeutic Context

2.1. Analysis of Condition

The proposed indication for Nayzilam is for the acute treatment of patients 12 years and older who required control of intermittent episodes of increased seizure activity, i.e., seizure clusters and acute repetitive seizures. Seizure clusters and acute repetitive seizures are used synonymously, and although not clearly defined as a condition by the International League Against Epilepsy, there have been several different proposed clinical and research definitions. For research purposes, the Agency has accepted the same definition that was previously utilized for the clinical trials of rectal diazepam in the treatment of acute repetitive seizures; seizure cluster is “an episode of multiple complex partial or generalized (tonic, clonic, tonic clonic, atypical absence, or myoclonic) seizures occurring within a 24-hour period in adults (12-hour period in children), with a pattern distinguishable from the patients’ usual seizure pattern, and with onset readily recognizable by a caregiver, such as a parent.”¹²

Although exact prevalence is unknown, especially given the sometimes-changing definitions, the prevalence of seizure clusters was recently estimated to be approximately 2.5/10,000 in a

¹ Peripheral and Central Nervous System Drugs Advisory Committee Meeting #45; November 15, 1996.

² Cereghino JJ, Mitchell WG, Murphy J, et al. Treating repetitive seizures with a rectal diazepam formulation. *Neurology* 1998; 51:1274-1282

recent UK study³. The most significant risk factor for incurring seizure clusters is having intractable epilepsy, or having a history of prior seizure clusters. Seizure clusters are primarily found in a subset of patients with epilepsy, and describe seizures of any type that occur in a group or cluster over a number of hours/days. Seizure clusters often result in emergency room visits with or without hospitalization, have negative impact on productivity, and are disruptive to daily life, including school and work, for both patients and their caregivers.⁴ Although seizure clusters may occasionally self-resolve, they often progress to prolonged seizures or status epilepticus⁵. Status epilepticus is a potentially life-threatening complication of seizure clusters, and early treatment is considered imperative to prevent such progression.⁶

Thus, the goals of seizure cluster treatment are seizure cessation and prevention of further seizures. Acute benzodiazepine treatment is considered the standard for effective and rapid seizure termination⁴. Available routes of administration for benzodiazepines include oral, buccal, sublingual, nasal, intramuscular, intravenous, and rectal. The widely available and approved parenteral formulations of lorazepam and diazepam are only able to be administered by EMS or ER personnel, and requires IV placement and transportation, often resulting in significant treatment delays. There are concerns regarding slower absorption and risk of aspiration when using the oral route for acute seizure treatment.⁴ Rectal diazepam is approved for use by caretakers for this situation, but is often not practical to administer, or may not be socially accepted by the patient or caregiver. Other off-label treatment options are the use of buccal lorazepam, diazepam, or intranasal or buccal midazolam. Non-rectal, non-IV routes of administration may be administered more rapidly than rectal or IV routes. Buccal midazolam is approved in Europe for children with acute seizure emergencies, and oral clonazepam is often used either buccally or sublingually, but has never been formally studied⁴. The literature also describes the use of the parental formulation of MDZ administered nasally or buccally via a needleless syringe. The current injection formulation is not optimized for nasal delivery, and low pH, larger volumes, may lead to lower efficacy, increased nasal toxicity, and/or lack of patient compliance. Patients may often prefer to forgo treatment and hope the seizure will resolve, rather than call EMS or utilize rectal diazepam.

2.2. Analysis of Current Treatment Options

The only FDA-approved drug treatment for the drug's proposed indication of acute repetitive seizures is rectal diazepam, also a benzodiazepine, which was approved as Diastat in 1996. The

³ Martinez, C, Sullivan T, Hauser WA. Prevalence of acute repetitive seizures (ARS) in the United Kingdom. *Epilepsy Res* 2009; 87:137-143.

⁴ Haut, SR. Seizure Clusters: characteristics and Treatment. *Curr Opin Neurol*. 2015; 28(2):143-50.

⁵ Mitchell WG. Status epilepticus and acute serial seizures in children. *J Child Neurol* 2002; 17(Suppl 1):S36-S43.

⁶ Cereghino, JJ. Identification and Treatment in Acute Repetitive Seizures in Children and Adults. *Curr Treat Options Neurol* (2007), 9: 249-255.

rectal route of administration is challenging for many patients and caretakers, and outside of very young children, is often not practical or socially acceptable, especially for administration outside of the home. It would be useful to have an alternate to rectal administration.

Although Diastat is the only approved medication for the treatment of seizure clusters, there are other benzodiazepines that are commonly used off-label for the treatment of seizure clusters, both in the outpatient setting, or for use upon arrival in the ER, or by EMS personnel. Commonly used treatments are oral midazolam, diazepam, lorazepam, and clonazepam, as well as IV/IM use of parenteral midazolam, diazepam, and lorazepam by EMS/ER. The injection forms of midazolam have also been administered intranasally and buccally, and the oral tablets of lorazepam are often crushed and administered buccally as well. These are all off-label uses of the drugs, as well as off-label routes of administration in ways other than the intended routes. All the above products are benzodiazepines.

The only non-drug treatment option is the FDA-approved Vagus Nerve Stimulator (VNS) Therapy System, which is indicated for use “as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications” and may occasionally be used for the treatment of seizures associated with seizure clusters.

Table 1 Table of Currently Approved Therapies Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed)
FDA Approved Treatments						
Diastat	Management of selected, refractory, patients with epilepsy who require intermittent use of diazepam to control bouts of increased seizure activity.	1997	Rectal, prn daily for seizure clusters, no more than 5 episodes per month, and no more than once every 5 days.	Median seizure frequency for the diazepam rectal gel treated group was 0 seizures per hour, compared to 0.3 seizure per hour for the placebo group, $P < 0.001$. Improvement in seizure frequency, severity, and “overall global assessment”	Risk from concomitant use with opioids, use with caution those with compromised respiratory function related to a concurrent disease process or neurologic damage, may interfere with cognitive/mot or performance,	Difficult to use in many situations/ages because of rectal route of administration, patient noncompliance.

				by caregivers. Also prolonged time to next seizure (p = 0.0002), and 62% were seizure-free compared to 20% who received placebo.	and used with caution in elderly, or those with impaired renal or hepatic function. Most frequent AE was somnolence, seen in 23% of patients.	
Other Treatments						
Benzodiazepines – Lorazepam, Diazepam, Midazolam, Clonazepam	Variable non-seizure indications (primarily sedation, anxiety) DZP and LZP indicated for status epilepticus in adults. DZP indicated for treatment of status epilepticus in pediatric patients.	Variable	Oral, injection, as well as non-intended uses such as buccal and intranasal	None, other than that described in literature	Class effect listed above regarding concomitant use with opioids or those with compromised respiratory function.	Off-label uses carry other associated risks, such as inaccurate dosing, risk of aspiration (oral/sublingual), difficulty with administration during a seizure, increased risk of nasal toxicity from parenteral formulation

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This 505(b)(2) application relies on the FDA's findings of safety and/or effectiveness for the listed drug and data from the published literature. The applicant is relying on the reference listed drug, NDA 0186652 "Versed injection", as well as the ANDA 075293 and the published literature.

Midazolam (MDZ) was approved in 1985 as an injection solution for use in adults for a variety of sedation and pre-anesthesia indications. It has never been indicated or marketed for the treatment of seizures or epilepsy. It has subsequently been approved for sedation in both adults and pediatric patients via additional routes of administration, including intramuscular injection, continuous intravenous infusion, and oral. It was recently approved for intramuscular injection for the pre-hospital (ER/EMS) acute treatment of status epilepticus in adults. MDZ is

also marketed in a buccal formulation over 50 non-US countries for the treatment of prolonged seizures.

3.2. Summary of Presubmission/Submission Regulatory Activity

See the below for timeline of key regulatory activity since the IND was initially opened in 2007.

2007 – IND 077421 opened by Ikano Therapeutics, Incorporated

2008 – Fast Track Designation granted

- At the time of fast track application, the applicant proposed (b) (4)

2009 – Orphan Drug Designation granted

2010 – IND was transferred to Upsher-Smith Laboratories (USL)

2010 – SPA agreed for pivotal study P261-401

- Of note, the SPA was later invalidated in 2014 because of modifications made after interim analysis.

2013 – EOP2 meeting

- Discussed the design of (b) (4) trial P261-301 for treatment of seizure clusters in patients admitted to an Epilepsy Monitoring Unit (EMU)
- Discussed the pediatric plan (PREA requirements do not apply given orphan drug designation)
- Emphasized that a test dose requirement for marketed use will be a future matter of review

2013 email correspondence

- FDA asked for the applicant to include data and literature addressing local intranasal mucosal toxicity and olfactory toxicity
- Required addition of olfactory testing for any future patients enrolled in the study

2015 Type C Meeting

- Discussed that the small number of patients with olfactory testing will be a matter of future review
- Discussed that because of study design, the applicant may not be able to demonstrate efficacy of 2nd dose

2016 Type C Meeting

- Determined that Study P261-301, (b) (4)
- Determined the applicant (b) (4) Studies P261-401 and P261-301
- After initial request, FDA did not recommend stopping P261-Study 401 early for reasons of slow enrollment

2017 – Correspondence

- P261-401 was stopped early for “business reasons” after completion of 201

patients

- Upshur-Smith transferred the product/studies to a newly formed subsidiary Proximagen, LLC

2017 – Type C Meeting

- Agency agreed that a single study has the potential to conclude effectiveness
- Determined that the data from Study P261-402 (open-label), Study P261-301 (b) (4) and open-label dose in Study P261-401 (b) (4) .
- For safety purposes, agreed that the total of 600 patients with at least one dose should be sufficient exposure

2018 – Pre-NDA Meeting

- Determined that (b) (4) is not possible for this indication
- Discussed that a need for REMS will be a matter of review
- Discussed that priority review will be a matter of review at time of submission

2018—Filing Meeting

- Division determined that they did not meet the criteria for priority review given that they did not provide a rationale in their NDA submission for priority review, (b) (4)

3.3. Foreign Regulatory Actions and Marketing History

Midazolam for intranasal administration for the treatment of seizures is not currently marketed in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

A clinical site inspection request was submitted to OSI. The clinical sites were chosen primarily based on numbers of enrolled subjects, impact on efficacy, and geographic area. The site selection information is presented in the Data Quality and Integrity Section of Section 6.1.2 Study Results.

4.2. Product Quality

See CMC review which was still pending completion at the time of this review.

4.3. Clinical Microbiology

Not applicable to this review.

4.4. Nonclinical Pharmacology/Toxicology

The applicant proposes to address the nonclinical requirements for approval by referencing the nonclinical studies from the listed reference drug midazolam for IM injection. The adequacy of the nonclinical studies will be addressed by the nonclinical review.

The nonclinical review by Dr. Ed Fisher was still pending completion at the time of this review.

4.5. Clinical Pharmacology

Please see the Clinical Pharmacology Review by Dr. Jagan Parapelly for complete details.

Overall, there were nine total Phase 1 studies that contributed to the pharmacokinetic and pharmacodynamic assessments, including studies in healthy subjects, a drug abuse liability study in patients with a history of recreational drug use, and studies in patients with epilepsy in the absence of a seizure. In the Phase 3 Studies P261-401 and P261-408, patients were administered study drug in the outpatient setting by a caregiver, and therefore, pharmacokinetic (PK) data is only available from the in-clinic test-dose phase which occurred in a monitored setting.

The applicant also conducted a Population PK (PopPK) analysis to provide further characterization of the PK profile of MDZ and its active metabolite 1-hydroxy-midazolam after IN administration, and is based on over 10,000 plasma samples collected from 602 patients from 6 of the clinical pharmacology studies and the 3 Phase 3 studies.

The clinical pharmacology section also included data from the reference listed drug and the available literature.

In summary, the applicant demonstrated that following MDZ NS administration,

- MDZ is consistently and extensively absorbed, demonstrated by measurable MDZ plasma concentrations by 5 minutes post-dose in most subjects and achievement of maximum observed plasma concentrations (C_{max}) within 10 to 15 minutes post dose.
- There is an estimated absolute bioavailability of approximately 44.4% and estimated of between-subject variability for MDZ exposure ranged from 16 – 39% demonstrating consistent absorption of MDZ.
- Approximate dose proportionality across the total dose range proposed (5 mg, 5 + 5 mg) for use in adults and adolescents with little to no increase in exposure observed at doses above this range, potentially providing a safety benefit by limited exposure in the case of accidental or intentional overdose.
- Lack of first pass metabolism with IN administration reduces the DDI potential (drug-

drug interaction) compared to oral administration.

- Across the total dose range studied (1.25 mg to 20 mg) MDZ apparent terminal half-life ranged from 2.1 to 6.2 hours and was independent of dose.
- Plasma concentrations of 1-OH-MDZ peaked later than MDZ (approximately 1 hour) because of the time required for metabolic formation by CYP3A4/3A5 in the liver.
- Consistent with being formed via hepatic metabolism of MDZ, similar dose-limited exposure to 1-OH-MDZ was observed.

The applicant proposes a bridge to the listed drug for the some of the pharmacokinetic (PK) properties.

- PK was similar in adolescent and adult subjects and adolescent age was not a significant covariate for efficacy or safety, therefore age not an important factor for dosing.
- Mean systemic exposures were 21-45% higher in geriatric subjects as compared to non-geriatric subjects. Elderly subjects may take longer to recover from the MDZ NS effects.
- No renal impairment studies done by the applicant, although the applicant provided literature to suggest that there would be higher exposures in patients with severe renal impairment.
- No studies on hepatic impairment were included in the application, but the labeling for the listed drug mentions reduced clearance in hepatic impairment.
- Drug-drug interactions were not studied.
- The PBPK modeling provided with the application was inadequate. The applicant did not respond to an information request (IR) sent by OCP in sufficient time to be considered during this review cycle.

4.6. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health (CDRH) provided a review of the device, including use data, reliability data, and validity data. The CDRH review recommends an approval action. Please refer to the full review for details.

4.7. Consumer Study Reviews

None performed.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 Listing of Clinical Trials Relevant to this NDA

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
P261-401 / NCT01390220	Phase 3, randomized, double-blind, placebo- controlled, parallel-group, multicenter (multinational) study	Test Dose Phase: two 5 mg USL261 doses (IN), 10 minutes apart (in absence of seizure) Comparative Dose Phase: 5 mg USL261 (IN) or placebo (IN), given during a seizure cluster. Optional open-label dose: 5 mg USL261 (IN) given after 10 minutes (and < 6 hours) if criteria met for second dose	Primary endpoint: Proportion of subjects with Treatment Success (seizure termination within 10 minutes AND no recurrence within 6 hours) Secondary endpoints: Proportion of subjects with recurrence of seizures within 4 hours; Time to next seizure with a start time > 10 minutes after drug administration; PK, Safety, and other Exploratory Efficacy Endpoints included	Test Dose phase: 2 doses 10 minutes apart Comparative dose phase: 1 or 2 doses for treatment of a single seizure cluster Follow-up: Within 1 week of comparative dose	Test dose phase: 292 Comparative dose phase: 201	≥ 12 years old with epilepsy and confirmed diagnosis of recognizable seizure clusters	105 sites in 11 countries; Canada (3), Australia (5), Germany (5), Hungary (4), Israel (6), Italy (6), New Zealand (2), Poland (6), Spain (7), Ukraine (8), USA (53)
<i>Studies to Support Safety</i>							
P261-402 / NCT01529034	Open-label, uncontrolled extension study	5 mg USL261 (IN) during a seizure cluster; second 5 mg USL216 (IN) dose may be given > 10 minutes to < 6 hours after first dose. Minimum of 3 days between seizure	Long-term safety and tolerability Secondary Endpoints: Termination of seizure(s) within 10 minutes and no recurrence within 6 hours	1-2 doses per seizure cluster. Duration variable for patient participation, up to 2 years.	161 patients	Age ≥ 12 years with epilepsy and confirmed diagnosis of seizure clusters who completed study P261-401	63 sites in 10 countries; Canada (1), Australia (4), Germany (4), Hungary (2), Israel (3), New Zealand (1),

Clinical Review
Emily R. Freilich, MD
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		clusters required.					Poland (4), Spain (4), Ukraine (6), USA (34)
P261-301 / NCT01999777	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multinational study	5 mg USL261 (IN) or Placebo (IN) during a seizure	Primary Endpoint: Number of patients that were seizure free (6 hours) Secondary Endpoints: Time to first seizure following treatment	Single 5 mg dose	62 patients	Age ≥ 12 years with epilepsy and increased seizure activity while in an Epilepsy Monitoring Unit (EMU) Setting	61 centers in 10 countries; Austria (3), Australia (2), Belgium (3), Czech Rep (2), France (1), Germany (5), Italy (2), Lithuania (1), Spain (3), USA (39)
P261-408 / NCT02161185	Open-label, single arm, safety study in the treatment of seizure clusters	5 mg USL261 (IN) dose during a seizure cluster, may repeat a second dose if indicated	Long-term safety and tolerability Secondary Endpoints: Termination of seizure(s) within 10 minutes and no recurrence within 6 hours	1-2 doses per seizure cluster, duration variable for patient participation	7 patients	Age ≥12 to 65 years, with epilepsy and a confirmed diagnosis of seizure clusters	16 centers in United States
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>							
P261-201 / EudraCT 77421	Randomized, double-blind, placebo-controlled, sequential dose-escalation inpatient study	Single dose: USL261 5 mg, 7.5 mg (IN) Placebo (IN) In absence of seizure Two-dose: Cohort 1: 10 mg (5 + 5) or placebo Cohort 2: 12.5 mg (5 + 7.5) or placebo	Safety, tolerability, pharmacokinetics, and pharmacodynamics of single and two-dose regimens of USL261 compared with placebo	Single dose, then two doses separated by 10 minutes; 3 days separation between dosing Up to 30 days duration	60 patients	Adult patients with epilepsy on stable antiepileptic drug (AED) regimens	Single center in United States

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Emily R. Freilich, MD
NDA 211321 Nayzilam (Intranasal midazolam)

		Cohort 3: 17.5 mg (10 + 7.5) or placebo Cohort 4: 20 mg (10 + 10) or placebo					
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Sources: Applicant-submitted Summary of Clinical studies, as well as Clinical study reports for Studies P261-401, P261-402, P261-301, P261-408, P261-201

5.2. Review Strategy

An efficacy determination was made by evaluating the results from the double-blind, controlled, comparative phase portion of the Study P261-401 (Study 401). This reviewer assessed the primary endpoint by examining the source data provided by the applicant. Statistical analysis of the data was performed and reported by Dr. Xiang Ling in her independent Statistical Review.

In 2017, the Division agreed that a single trial, if positive and robust, would be sufficient for demonstration of efficacy, because of the known class effect of benzodiazepines demonstrating consistent efficacy among different seizure types, including status epilepticus, as well as prior approval of rectal diazepam for the proposed indication of seizure clusters. Since the submission of the NDA, intramuscular MDZ (Seizalam) for the pre-hospital treatment for status epilepticus in adults was also approved, lending further support to the effectiveness of MDZ in some seizure disorders.

A safety determination was made by evaluating the safety data from the pivotal trial, in both the comparative phase, and open-label test dose phase, as well as safety data from (b) (4) inpatient study (P261-301), and two open-label safety and tolerability studies (P261-402 and P261-408). Safety data from some of the key Phase 1 studies was also reviewed. See Section 8.1.

The submitted published literature was also reviewed for supportive evidence of effectiveness and safety, as well as the available literature on the olfactory and nasal toxicity of the use of intranasal midazolam.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. P261-401 – 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)

6.1.1. Study Design

Overview and Objective

Study 401 is a Phase 3 study of intranasal midazolam (USL261 = MDZ NS) in patients age ≥ 12 years with epilepsy and a documented history of seizure clusters that are recognizably different from the patient's other non-cluster seizure activity.

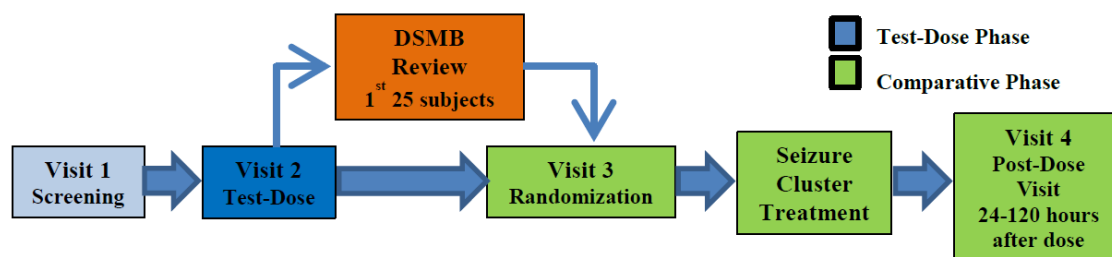
The primary objectives of the study were to evaluate the efficacy of MDZ NS compared with that of intranasal placebo for the outpatient treatment of seizure clusters with secondary objectives to evaluate the safety and tolerability of MDZ NS in the outpatient treatment of seizure clusters, as well as the pharmacokinetic profile of MDZ NS.

Trial Design

- Basic Study Design

The study was a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group design with 2 distinct phases, and 4 planned study center visits, as seen in Figure 1.

Figure 1 Planned Study Design and Schedule of Assessments



The first phase of the study was an open-label “Test-Dose Phase” in a monitored unit to evaluate the tolerability of the drug while patients were not actively having a seizure cluster, and the second phase was the “Comparative Phase” in which patients were randomized to receive either 5 mg MDZ NS or placebo by a trained caregiver, during a seizure cluster, in an outpatient, community setting.

Initially the Test-Dose Phase included monitoring of the patient for at least 4 hours in the study center. However, after the first 132 patients had completed the Comparative Phase, a protocol amendment reduced the observation period after the test dose from 4 hours to 1 hour.

The test dose was administered at Visit 2, which was within 28 days of Screening (Visit 1) and required caregiver training in treatment administration, CPR, and airway management techniques before test dose was given. Visit 3 occurred within 24 hours to 28 days of Visit 2, with the exception of the first 25 patients who required DSMB review prior to the study proceeding to Visit 3. At Visit 3, patients were randomized in a 2:1 MDZ NS to placebo, caregivers would demonstrate their hands-on competence in not only administering the study drug, but also performing timed respiration rate measurements, recording them, and demonstrating airway management techniques.

Each patient was given a patient management plan (PMP) that was an individualized treatment algorithm with rescue protocol for the caregiver to follow with treatment of the next seizure cluster. Study-drug administration would occur on an outpatient basis at the time of the patient's next eligible seizure cluster (per their PMP), and then Visit 4, the Post-dose visit, was scheduled to occur between 24 and 120 hours after study drug administration.

- **Trial Location**
Study 401 was conducted at 103 centers in 11 countries. Overall, the patient population is expected to be similar to, and therefore, generalizable to the patient population in the United States.
- **Choice of Control Group**
The applicant used a concurrent placebo control as the comparator group as recommended in FDA guidelines for demonstration of effectiveness. Comparison to placebo is an appropriate control arm for this study to demonstrate effectiveness in the indicated condition. A comparison could have been done to the approved treatment Diastat (rectal diazepam); however, the applicant's position is that MDZ NS is an improvement over currently available therapies because of the ease of use/convenience of route of administration, and that demonstrating of superior efficacy was not necessary.

Reviewer's comment: Of note, the trial design appropriately uses a concurrent placebo control to demonstrate effectiveness. However, the patients were all given an option of taking a second, "open-label", active dose if there was no improvement from the initial treatment. The applicant acknowledges that the design could lead to "progression bias" because caregivers and patients may have administered the second dose sooner knowing it was active drug and wanting to make sure they received it. For this reason, patients were randomized in a ratio of 2:1 active drug: placebo to try to minimize the implications of this effect. The open-label second dose study design also reduces the number of patients who truly received "placebo", and makes it challenging to determine any efficacy of the second dose.

- **Diagnostic Criteria**
The diagnostic criteria for admission into the study were identified in the inclusion criteria as the following:
 - Established diagnosis of partial or generalized epilepsy that included all the following:
 - Documented history of seizure clusters lasting a minimum of 10 minutes from the time the seizure cluster is recognized
 - Seizure cluster pattern was observable, stereotyped, and recognizably different from the patient's other non-cluster seizure activity (if any) in

- seizure type, duration, severity or frequency
 - As part of the patient's stereotyped seizure cluster pattern, a second seizure typically occurred within 6 hours from the time of recognition of the seizure cluster
 - In the investigator's opinion, it was safe for the patient to receive placebo as a first dose of study drug followed by active treatment as the second dose of study drug no earlier than 10 minutes after the first dose
 - The patient's stereotyped seizure cluster pattern was composed of multiple (≥ 2) partial or generalized seizures
 - The patient's stereotyped seizure cluster pattern was established > 3 months before Visit 1
- A frequency of ≥ 3 stereotyped seizure clusters during the year before Visit 1
 - At least 1 stereotyped seizure cluster occurring ≤ 4 months before Visit 1
 - The seizure cluster pattern described above was confirmed by a central reviewer
- Key inclusion/Exclusion criteria

Inclusion criteria

- Patient has a competent, adult caregiver who was able to recognize and observe the patient's seizure cluster episodes, and was willing to be trained in the study procedures
- Age ≥ 12 years at Visit 1
- Patient was receiving a stable regiment of AED(s) since Visit 1 and for ≥ 7 days before Visit 2. Changes in dose of an AED were allowed during the study; however, the new dose level was required to be kept stable for at least 7 days before study drug received.
- Benzodiazepines used for rescue therapy for seizures or for non-epilepsy indications were allowed *provided* they were typically used ≤ 3 days in a 7-day period on average and always at the same dose. Daily use of a benzodiazepine as a chronic AED was not permitted.
- Patients had to have a diagnosis of partial or generalized epilepsy, with a history of documented seizure clusters that were observable, stereotyped, and recognizably different from the patient's other non-cluster seizure activity as described above under Diagnostic Criteria.
- Documented head imaging that confirmed absence of a progressive neurological disorder
- Weight of 40 kg to 125 kg (inclusive)

Key Exclusion Criteria

- Acute narrow-angle glaucoma
- Uncontrolled medical condition or progressive neurological disorder

- Severe chronic cardiorespiratory disease with baseline room air oxygen saturations < 90% or the need for ambulatory oxygen
- Psychogenic, non-epileptic seizure(s) within the 5 years, a major depressive episode anytime within 6 months, or history of or active suicidality
- Psychosis in the 12 months before Visit 1, excluding postictal psychosis
- History of stereotypical seizure cluster (for which they were being enrolled in the study) progressing to status epilepticus within the 2 years before Visit 1
- History of drug or alcohol abuse within 1 year before Visit 1
- Known allergy to midazolam
- Any clinically significant laboratory abnormality as determined by the investigator and as confirmed by repeat testing, or any of the following abnormalities at visit 1:
 - Phenobarbital concentration > 35 µg/mL
 - ALT/AST > 2x the upper limit of normal
 - White blood cell count > 2.5 x 10⁹/L
 - Sodium < 128 mEq/L
 - Creatinine > 2.0 mg/dL

Patients further excluded at Visit 2 if:

- Patient had active suicidal plan/intent or suicidal thoughts as defined by a C-SSRS suicidal ideation score ≥ 3 or had suicide attempt since the last visit
- Patient had a positive pregnancy test
- Consumed any clinically significant CYP450 3A inhibitor/inducer, opioid, or other respiratory depressant (excluding AEDs) within the required washout period before Visit 2
- Any of the following during the 4 hours after administration of the MDZ NS test dose:
 - Blood pressure
 - SBP < 85 mmHg and the change from baseline (pre-dose evaluation) in SBP was deemed clinically significant by the investigator
 - A ≥ 40 mmHg change from baseline in SBP
 - DBP < 50 mm Hg and the change from baseline (pre-dose evaluation) in DBP was deemed clinically significant by the investigator
 - A ≥ 30 mm Hg change from baseline in DBP
 - Heart rate
 - HR > 120 or < 50 bpm and change from baseline (pre-dose evaluation) in HR was deemed clinically significant by the investigator
 - A ≥ 40 bpm change from baseline
 - Respiratory Rate

- RR > 24 breaths per minute and change from baseline in RR was deemed clinically significant by the investigator
- RR < 8 breaths per minute while awake or after arousing
- Sedation to the degree that the patient did not respond to mild prodding or shaking
- Oxygen saturation < 90% for > 30 seconds or required oxygen at any time
- Clinically significant ECG findings as determined by the investigator

Patients Further Excluded at Visit 3 (Randomization) if:

- Patient developed a new medical condition or required a new treatment that met any previously described study exclusion criteria
- Patient had a positive pregnancy test
- Patient had an active suicidal plan/intent or suicidal thoughts as defined by a C-SSRS suicidal ideation score ≥ 3 or had a suicide attempt since last visit

Reviewer's comment: The designated inclusion and exclusion criteria were appropriate for the proposed study population of patients with partial or generalized epilepsy who experienced recognizable seizure clusters. The exclusion criteria outlined above for Visit 2 and Visit 3 are essentially the same as the stopping criteria following the Test Dose to specify which patients were allowed to move on to Visit 3 and Randomization.

- Dose Selection

The dose selection was based on earlier PK assessments and safety data from two earlier PK trials in adults, as well as the extensive published literature. The maximum dose of 10 mg of MDZ within a 6-hour time period was well within the range of doses that correlated with efficacy and appeared to be safe based on the published literature.

- Study Treatments

In the Test Dose Phase, all patients received two 5 mg doses of MDZ NS administered intranasally 10 minutes apart at the study center. In the Comparative Phase, patients were randomized to receive either 5 mg MDZ NS or placebo (2:1), administered intranasally by a caregiver during a seizure cluster that met the study criteria. Patients with persistent or recurrent seizure activity after receiving the double-blind study drug had the option of administering a 5 mg open-label dose of MDZ NS between 10 minutes and 6 hours after the initial dose, provided there was no evidence of excessive, uncharacteristic, marked sedation, the patient did not have a respiratory rate < 8 breaths per minute, and the patient did not require emergency rescue treatment with assisted breathing or intubation.

Each patient had an individualized patient management plan (PMP), prepared by the investigator, which described the type of seizure cluster eligible for treatment with the 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, and a rescue protocol for persistent or recurrent seizure activity or other

safety concerns. The PMP was provided to an expert Central Reviewer within the Epilepsy consortium for final determination of whether the patient qualified for the study. The PMP also indicated what the caregiver should do if the seizure activity persisted, when to call EMS, and assisted the central study nurse in helping the caregiver complete the study assessments after doses were given.

- Assignment to Treatment

Patients were randomized to MDZ NS or placebo in a 2:1 ratio. At Visit 1, the investigator contacted the Interactive Response Technology System (IRT) to register the patient. At Visit 2, the investigator contacted IRT to confirm the administration of the test dose. At Visit 3, all patients meeting the eligibility criteria were randomized (2:1) to receive MDZ NS or placebo using IRT, and then the investigator obtained a drug kit number via IRT. The instruction on access and use of the IRT services was detailed in the IRT manual. The randomization code was generated by an unblinded statistician at the CRO ((b) (4)), who was not otherwise involved in the study. The randomization was generated using fixed blocks and was stratified only by age (< 18 years and ≥ 18 years). The applicant did not have access to the randomization code until after the database lock.

- Blinding

For the initial dose in the Comparative Phase, drug supplies were blinded in a double-blind fashion with information including the protocol number, kit identification number, and instructions for use. The drug name did not appear on the label. MDZ NS was not blinded for the Test Dose Phase or for the open-label second dose provided to patients during the Comparative Phase.

Both active and placebo drug utilized a Unit-Dose Nasal Spray System consisting of a stoppered glass vial containing study drug inserted into a vial holder, which is in turn held in a white plastic nasal spray actuator. The dosage unit contained sufficient solution to provide a single 5 mg dose of MDZ NS and overfill for the pump to work correctly. The placebo nasal spray consistent of the same inactive ingredients as found in MDZ NS; actuation of the pump delivers 0.1 mL of the solution.

- Dose modification, Dose Discontinuation

There were no pre-specified dose modifications or reductions in the protocol. The reasons for discontinuation after the Test Dose are outlined in the exclusion criteria above.

- Administrative Structure

The study was sponsored by the former sponsor, Upsher-Smith Laboratories, Inc (USL) Maple Grove, Minnesota, and was conducted by an independent CRO, (b) (4) . The writing of the clinical study report was sponsored by Proximagen, LLC, a subsidiary of USL, who assumed sponsorship of the product after the completion of the clinical conduct.

The study was conducted at 103 centers in 11 countries, listed in Section 5.1 / Table 2 above.

A Data and Safety Monitoring Board (DSMB) was utilized to review the safety of the study after the first 25 patients received the Test Dose, as well as any unexpected adverse events that occurred during the study. The DSMB also reviewed the safety data at the time of the interim analyses, after 132 and 165 patients had completed the Comparative Phase. There was also an Interim Analysis Monitoring Committee (IAMC) that was independent of the sponsor and conducted the interim analyses.

- Procedures and Schedule

The following table summarizes the schedule of study visits and includes key assessments that occurred at or between those visits.

Table 3 Schedule of Key Study Procedures

Phase	Screening	Test Dose	Comparative Dose		
Visit Number	1	2	3	Treatment ^a	4 or ET ^b
Study Assessments					
Inclusion/Exclusion evaluation	X	X	X		
Caregiver Training ^c	X	X	X		
Concomitant Medication Review	X	X	X		X
B-SIT ^d (US only)		X	X		X
Pregnancy Testing	X	X	X		X
Clinical laboratory testing	X				X
Randomization			X		
Treatment Administration		X		X	
PK Blood Sampling		X			
OAA/S ^e		X			
Caregiver-recorded Respiration Rate ^f		X		X	
12-lead ECG	X	X	X		X
Vital signs	X	X	X		X
C-SSRS ^g	X	X	X		X
Record sz activity in Subject Workbook				X	
Adverse Event Collection	X	X	X	X	X
Telephone follow-up				X ^h	

Source: Reviewer's summary of Schedule of Procedures, Study 401 CSR, Table 2

^a No visit at the time of outpatient study drug administration. Post-dose visit 4 occurred 24 - 120 hours after study drug administration.

^b ET = Early Termination Visit. Any patient who had not treated a seizure cluster within 6 months of Visit 3 (randomization) returned to the study center for Visit 4 (Early Termination).

^c Caregiver training included, but not limited to, providing self-study training with review of that training by the personnel, as well as CPR and airway management training for caregivers.

^d B-Sit = Brief Smell Identification Test

^e OAA/S = Observer's Assessment of Alertness/Sedation Scale

^f Caregivers counted number of breaths taken by the subject during a 30-second interval at Visit 2 (before, and at 5, 10, 15, 20, 30, 45 minutes, and 1, 1.5, 2, 3, and 4 hours after first test dose), and on day of treatment (approximately 15 and 30 minutes, and 1, 2, and 4 hours after drug administration).

^g C-SSRS = Columbia Suicide Severity Rating Scale

^h After Visit 3, telephone follow-up phone calls with the patient or patient's caregiver/LAR occurred monthly until Visit 4 / ET. Caregivers were to call the central study nurse hotline as soon as possible after administering the study drug.

- Dietary Restrictions/Instructions

There were no activity restrictions required by this study.

Food and beverages not permitted during this study included grapefruit, grapefruit juice, Seville oranges, and star fruit, as they may have altered the patients' response to treatment.

If a patient did consume any of these substances, the patient was instructed to wait the minimum washout period for the time between the last dose of that substance and the date allowable to resume study drug treatment for a qualifying seizure cluster.

- Concurrent Medications

Prior medications were defined as any medication, nutritional supplement, herbal preparation, or device (e.g., VNS) taken or used within 30 days prior to the first dose of study drug at Visit 2. Concomitant medications were defined as any medication (or supplement, as above), taken or used from Visit 2 through Visit 4/end of treatment.

A patient's AED regimen must have been stable with no changes in drug type from Visit 1 through Visit 4/end of treatment, and for ≥ 7 days before Visit 2. Changes in the dose of an AED were allowed during the study; however, the new dose level must have been stable for at least 7 days prior to receiving study drug in both the Test Dose and Comparative Phases. VNS settings were kept stable throughout the study period and each use of VNS was documented in the Subject Workbook.

The use of sedating antihistamines and alcohol were allowed during the study treatment period; however, the patient and caregiver were instructed that they were not to be used for at least 24 hours after study drug administration and study drug was not to be administered within 24 hours after taking a sedating antihistamine or alcohol.

The prohibited medications from Visit 1 through Visit 4 included CYP3A4 inhibitors/inducers, opioids, and other non-AED respiratory depressants. Any use of these medications prior to Visit 1 required a minimum washout time period specified prior to receiving the study drug in Visit 2. If a patient used one of these medications and its use was temporary and not recurrent, then a patient could have waited a minimum washout time period prior to using the study medication in a qualifying seizure cluster. If use of one of these medications was either chronic or recurrent, then the patient was to be discontinued from the study.

Furthermore, the use of benzodiazepines for rescue therapy or non-epilepsy indications were allowed provided they were used typically ≤ 3 days in a 7-day period on average and

always at the same dose. Benzodiazepines for rescue therapy of seizures or non-epilepsy indications were not to be used within 24 hours PRIOR to study drug administration and not for at least 6 hours AFTER study drug administration, as outlined in the patient's individual PMP. Benzodiazepines were not allowed as a chronic AED during the study.

- Treatment compliance

Outpatient treatment compliance was determined by the return of used and unused study drug, as well as the dosing information recorded in the patient's Subject Workbook.

- Rescue medication

If the patient encountered persistent seizure cluster activity or seizure recurrence, after the initial double-blind study drug dose, caregivers were instructed to give an open-label 5 mg MDZ NS dose, provided that it was at least 10 minutes and < 6 hours after initial study drug dose. If the patient continued to have persistent seizure activity or recurrence, had < 8 breaths per minutes, or was excessively and uncharacteristically sedated, then the caregivers were instructed to follow the rescue protocol outlined in the patient's individualized PMP, including when and how to contact EMS. As above, benzodiazepines were not to be used for 24 hours prior to and at least 6 hours after, study drug administration.

- Subject Completion, Discontinuation, or Withdrawal

Patients could withdraw from participation in the study at any time for any reason. If the caregiver withdrew from the study without a suitable, trained replacement, then the patient was discontinued from the study. A patient who prematurely discontinued from study participation should have returned for an early termination (ET) visit evaluation.

If a patient met the protocol-defined exclusion criteria after test dose administration because of meeting one of the safety parameters, then the patient was discontinued from the study and a corresponding AE was recorded.

The primary reason for a patient's premature discontinuation from study participation was selected from the standard categories listed below:

- Adverse Event
- Withdrawal of consent (Patient or Caregiver desires to withdraw from further participation)
- Lost to Follow-up
- Protocol violation
- Patient has not experienced a seizure cluster meeting study criteria within 6 months after randomization
- Patient pregnancy
- Administration/Other

If patients received the double-blind dose in the comparative phase and completed Visit 4 they were considered a study completer. Patients that discontinued after the test dose phase and were not randomized, or did not receive a double-blind dose in the comparative phase were not included in the efficacy analyses, as they were not in the mITT population, and this was specified in the SAP. Patients were not replaced if they withdrew after receiving a double-blind treatment dose.

Study Endpoints

- Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of patients who met the criteria for Treatment Success for the seizure cluster that was treated during the Comparative Phase, which was defined as achieving both of 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.

Any patient who received a second dose of study drug within 6 hours of the first dose during the Comparative Phase did not meet the definition of a Treatment Success.

Reviewer's comment: The primary endpoint was discussed and agreed to during SPA discussions in 2013. The choice of endpoint and the time frame for assessment of the endpoint seems appropriate for the proposed seizure cluster indication. The only other approved drug for a similar indication is rectal diazepam, and the primary endpoint of those trials was seizure frequency during the period of observation (12-24 hours) and a global assessment of the severity and nature of the seizures as well as their frequency. There are no other similar trials in acute repetitive seizures or seizure clusters.

Although a composite endpoint, both components have similar clinical importance and weight towards efficacy, and the study is well-designed to capture both endpoints. Both endpoints had to be met to be declared a treatment success. Given the definition of seizure clusters, many of the seizures may stop on their own after a short period of time and then recur, so seizure termination at 10 minutes, while important, is not sufficient. However, lack of seizure recurrence from 10 minutes to 6 hours is also significant and is perhaps even more clinically meaningful in this indication/patient population.

The Agency agreed to the study design and primary endpoint, which was initiated under SPA and agreed on October 29, 2012. The Agency rescinded the SPA on April 17, 2015, because of the applicant's decision to implement a proposed increased in study sample size and the addition of 3 interim analyses without agreement of the changes (see Sample Size Justification below). Subsequently, I note that Study 401 was terminated early because of business reasons in February 2017.

- Secondary Endpoints
 - Proportion of subjects with recurrence of seizure(s) beginning 10 minutes after dosing to 4 hours after dosing
 - Time to next seizure with a start time > 10 minutes after dosing
- Exploratory Endpoints:
 - Proportion of patients with recurrence of seizures beginning 10 minutes after study drug administration to 24 hours after study drug administration
 - Time to return to full baseline functionality (as determined by caregiver)
 - Analyses for subjects receiving 2 doses of MDZ NS
 - Subject and caregiver outcome assessments including:
 - SF-12v2, 8 domains, summarization and analysis for the mITT and the randomized population
 - TSQM – treatment satisfaction questionnaire for the medication, 14 items administered to the patient
 - Intranasal therapy impact questionnaire

Reviewer's comment: Of note, all seizure types that occurred within 24 hours were recorded because MDZ NS was expected to have activity against all types of seizures, it may have been difficult to determine if subsequent recurrent seizures were of the same type as those prior to the acute treatment.

- Safety Objective

The safety and tolerability of MDZ NS for the treatment of seizure clusters were assessed using the following parameters:

- Adverse Events
- Caregiver-recorder respiration rate at 15 minutes, 30 minutes, 1 hour, 2 hours and 4 hours
- Clinical laboratory tests
- Vital sign measurements as recorded by the study center personnel
- Physical, nasal, and neurological examinations
- Brief Smell Identification Test (B-SIT, US sites only)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Observer's Assessment of Alertness/Sedation Scale (OAA/S)
- Requirement for unscheduled emergency room (ER) or Emergency Medical services (EMS) within 24 hours after study drug administration

- Pharmacokinetics Objective

The pharmacokinetic (PK) objective was to evaluate the PK profile of MDZ NS after administration of MDZ NS 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
- λ_z - the terminal elimination rate constant
- T_{lag} - the time before the first measurable plasma concentration
- CL/F - apparent clearance
- V_z/F - volume of distribution

Given that the PK sampling schedule was limited to only 4 hours post-dose in the Test dose phase, insufficient samples were available for estimation of the terminal rate constant, λ_z . Therefore, λ_z and associated parameters (terminal half-life, $AUC_{0-\infty}$, CL/F , and V_z/F were not calculated.

Statistical Analysis Plan

The original statistical analysis plan (SAP) as dated April 11, 2013. There were 3 amendments sent to the FDA and the 2017 version (April 14 2017) was finalized prior to database lock.

Primary Endpoint Analysis

The primary analyses used the modified intent-to-treat (mITT) population, which included all patients who were randomized and received at least 1 dose of double-blind study drug in the comparative phase, and who had any post-treatment efficacy assessments. The per-protocol population (PPP) was used for supportive analyses to assess robustness of primary analysis.

The analysis of the primary efficacy endpoint (treatment success) and its components (seizure termination and recurrence) were analyzed using Fisher's exact test. A chi-squared test was performed as a sensitivity analysis.

The other relevant analysis populations are outlined below:

- Safety population - includes all patients who received at least 1 dose of study drug, even those who were not randomized. This includes all treated patients.
- Randomized population (intent-to-treat, or ITT) – includes all patients who were randomized to receive double-blind treatment.
- Randomized safety population (RSAF) – includes all patients who were randomized and received at least 1 dose of double-blind study drug. These patients were also included in the mITT population.
- Per-protocol population (PPP) – includes all patients in the mITT population who had not discontinued prematurely and had not had any excludable protocol deviations. Of note, all deviations were reviewed in a blinded manner and determined if would be excluded from the PPP prior to the database lock and unblinding.

Reviewer's comment: All the efficacy analyses used the mITT population according to randomized treatment assignment. Many patients were randomized but did not actually receive the study drug in the comparative phase, mostly because of not having an eligible seizure cluster in the specified time period. The potential bias of excluding those patients who were randomized but did not receive study drug was negligible since exclusion was not influenced by knowledge of assignment to treatment arm.

Sensitivity Analyses/Baseline Covariates

A sensitivity analysis was conducted using Cochran-Mantel-Haenzsel (CMH) test stratified by age. Exploratory logistic regression on treatment success was conducted with a backward selection of covariates in which covariates with a $P > 0.10$ were dropped from the model. The following covariates were used:

- Age
- Sex
- Weight
- BMI standardized categories
- Geographic Region of clinical site
- Enzyme-inducing AEDs used within 14 days prior to study drug administration vs others

Definition of a completer

Patients were considered completers if they received a dose in the double-blind comparative dose phase and returned for their Visit 4 follow-up visit.

Key Secondary Endpoint Analysis

All secondary endpoint analyses were based on the mITT population with multiplicity adjustments described below.

The time to next seizure with start time > 10 minutes after study drug administration was analyzed by log-rank test. Patients who did not have another seizure before the end of the 24-hour observation period and were not administered the second dose of study drug were censored at the end of the observation period. Patients who were administered the second dose of study drug but who did not have a seizure before the administration of the second dose would be censored at the time of the second dose.

The proportion of patients with recurrence of seizure beginning 10 minutes after administration of the double-blind study drug to 4 hours after dose of study drug was analyzed using Fisher's Exact Test. A chi-squared test was performed as a sensitivity analysis. Any patient who received the second dose of study drug within 4 hours of double-blind study drug administration were counted as if they had a seizure recurrence.

To control Type 1 error for the primary and secondary efficacy endpoints a statistical gate-

keeping procedure was applied to control for multiplicity. The primary and secondary efficacy endpoints were tested individually using the following hierarchical procedure. To proceed to the next step in hierarchy, the previous step was required to be statistically significant:

- Step one: the proportion of patients that were classified as treatment success during the comparative phase (2-sided p-value) was determined.
- Step two: the secondary endpoint of time to next seizure following first dose of study drug was determined using the p-value from the log-rank test.
- Step three: the proportion of patients with recurrence of seizure beginning at 10 minutes after study drug to < 4 hours following first dose was determined.

Handling of missing data

Observed data were presented in tables and listing without imputation of missing values, unless otherwise stated. If data was not sufficient to confirm classification as either Treatment Success or Not a Treatment Success, then the patient was considered to have missing data. For primary analysis, patients with missing data impacting determination of treatment success or its components were considered as "not a treatment success".

Reviewer's comment: No patients had missing data in the study.

Interim Analysis /Multiplicity Adjustment

After the applicant increased the sample size to a maximum of 240 completed patients, the applicant planned three interim analyses to evaluate the treatment success rate for possible early stopping for success or futility, after completion of 132, 165, and 204 patients. Analyses were conducted and reviewed by an unblinded Interim Analysis Monitoring Committee (IAMC), independent of both the applicant and the DSMB. Each interim analysis was to be performed on the mITT population during the Comparative Phase.

The trial was to be stopped for futility if the predictive probability for success at the maximum sample size was less than 10%. At each interim analysis, a one-sided Fisher's Exact test on the two proportions was to be performed and compared to the Lan-DeMets Pococks approximation boundary critical values, seen in Table 4.

Table 4 Success Boundary Values for Interim Analyses

Interim Analysis	p-Value
n = 132	0.0166
n = 165	0.0094
n = 204	0.0089
n = 240	0.0085

Source: Study 401 CSR

Based on this Lan-DeMets spending function approximation of the Pocock boundary, the 1-sided p-value required for success for the final analysis at the maximum sample size of 240 was 0.0085. Two interim analyses were conducted. Interim analysis #1 ($n = 132$, $p = 0.1644$) on and Interim Analysis # 2 ($n = 165$; $p = 0.0293$) did not meet the threshold criteria for stopping the trial for early success or for futility. The applicant ended the study based on business reasons not related to safety or efficacy, and the third planned analysis was not done. However, the applicant proposed a conservative statistical approach to conduct the final analyses with all available patients ($n = 201$) using the p-value of 0.0085 which is what would have been required for study success at the final analysis of the target 240 completed patients, had the third interim analysis been performed.

Reviewer's comment: As noted in Dr. Ling's Biometrics Review, the Type I error control for secondary endpoints was achieved by a hierarchical testing procedure, described above. The SAP did not clearly specify the significant level for the secondary endpoints. However, the secondary endpoints did not have the full alpha of 0.05 (2-sided) because of the interim analyses conducted.

Sample Size Justification

The original study design planned for 132 completed patients. However, an emergent publication during the study reported a higher placebo response rate than initially calculated⁷, prompting the applicant to conduct a meta-analysis based on odds ratio on the pooled data from a well-controlled study of intramuscular(IM) diazepam, and the two well-controlled studies of rectal diazepam that were used as the basis for the original protocol design. The applicant felt that the new calculations would have left the power at 75%, much lower than the targeted 90% power. Therefore, the study was adjusted to plan for 350 patients enrolled in the test dose phase to maximize a sample size of 240, and the sequential interim analyses described above were planned.

Protocol Amendments

The original protocol was dated March 30, 2011. It was amended 5 times, but the last amendment was not implemented. There were also 5 protocol clarification letters. These changes are summarized below in Table 5.

⁷ Abou-Khalil B, Wheless J, Rogin J, et al. A Double-blind, Randomized, Placebo-controlled Trial of a Diazepam Auto-injector Administered by Caregivers To Patients with Epilepsy who Require Intermittent Intervention for Acute Repetitive Seizures Epilepsia; 2013: 1-9

Table 5 Summary of Major Protocol Amendments, Study P261-401

Amendment Number	Date	Major Changes
1	19 December 2012	<ul style="list-style-type: none"> Clarified the definition of recurrence of seizures and expanded the time period for the primary endpoint for recurrence of seizures from 4 hours to 6 hours Replaced the term “respiratory depression” with a list of individual assessments already being used to measure respiratory effects Decreased minimum weight from 50 to 40 kg, removed restrictions on some prohibited drugs, and added exclusion criteria for blood pressure/heart rate Clarified statistical methodology
2	20 October 2014	<ul style="list-style-type: none"> Modified the trial to utilize a group sequential design with 3 interim analyses and a maximum of approximately 240 subjects Lower age decreased from 14 to 12 years of age, upper age restriction removed. Reduced minimum observation time at Test Dose Visit from 4 hours to 1 hour Reduced AE reporting from 30 days after drug administration to 7 days Clarified that subjects without enough available data to confirm Treatment Success/Not Treatment Success were considered missing data
3	26 February 2015	<ul style="list-style-type: none"> Updated the definition of the mITT to maintain the wording in the original protocol Updated statistical analysis of the primary efficacy endpoint to maintain the analyses in the original protocol and add chi-squared test as a sensitivity analysis
4	20 May 2015	<ul style="list-style-type: none"> Added B-SIT to assess effects on olfaction Added collection of the number of calls to EMS/ER visits for a seizure cluster
5	13 July 2016	(b) (4)

Source: Adapted from Study 401 CSR

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant has provided attestation that Study P261-401 were conducted in accordance with the CFR governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice.

Financial Disclosure

Per the submitted Form 3454, there were no financial disclosures to report for the applicant or

any of the clinical investigators for any of the covered clinical studies.

Patient Disposition

A total of 402 patients were screened for Study 401, and 292 patients entered the Test Dose Phase (Table 6). Of these, 262 patients were randomized into the Comparative Phase (174 MDZ NS, and 88 placebo), and a total of 201 patients received a double-blind treatment in the Comparative Phase (randomized safety population, RSAF). The RSAF included 134 patients who received MDZ NS in the Comparative Phase, and 67 patients who received placebo. Of the 201 patients in the RSAF who received the study drug in the Comparative Phase, 200 completed the study.

Table 6 Patient Disposition for Study P261-401

Screened Population	402
Screen Failures	110
Safety Population	292
Not randomized	30
Randomized Population	262
Randomized Safety Population (= mITT Population)	201
Per Protocol population	189
Completed Study	200
Discontinued Prematurely	92
Not randomized	30
Not dosed in Comparative Phase	61
Withdrew consent after dosing	1

Source: Reviewer adapted from Study 401 CSR Table 14.1.1.1

Of the 92 patients who discontinued from the study, 30 of them were never randomized, and 62 patients were randomized but did not complete the study. One of these patients withdrew consent after dosing, completed the post-treatment efficacy assessments and is included in the mITT population. The other 61 patients were discontinued prior to dosing in the Comparative Phase. Reasons for discontinuation are summarized in Table 7.

Table 7 Disposition of patients that did not complete study (N = 92)

Disposition	Received test dose but not Randomized (N = 30)	Randomized but did not receive dose in Comparative Phase (N = 62)*
Adverse Event	14	3
Withdrew Consent	3	*7
Lost to Follow-Up	1	1
Protocol Violation	6	2
Pregnancy	0	0
Other	6	49
No seizure cluster in time frame specified	0	37
Caregiver no longer available	0	5
Study drug unavailable at site	2	1
Study Terminated	1	4
Site Closure	0	1
Other**	3	1

Source: Reviewer adapted from Study 401 CSR, Table 14.1.1.2, 14.1.1.3, 14.1.1.4

*A single patient was randomized, received a dose in comparative dose phase, and then withdrew consent prior to study completion and is included here. This patient is included in the mITT population.

** Other reasons include met Exclusion Criteria 2, 6, 27 (Received test dose not randomized), and Sponsor Request

Reviewer's note: It is usually a concern if a large number of patients are randomized but not included in the primary analysis. However, because of the particular study design, many patients were randomized into the Comparative Phase but did not ever receive a double-blind study drug treatment for various reasons, and thus were not included in the mITT population. The majority of these patients did not have a seizure cluster in the specified time period, and were discontinued from the study. No patients who received drug in the double-blind phase were then excluded from the primary analysis/mITT population. As noted above, the single patient who withdrew consent after receiving a double-blind study drug dose in the comparative phase is included in the primary efficacy analysis.

Furthermore, those patients that were randomized but not dosed in the Comparative Phase included 41 patients randomized to MDZ NS, and 21 randomized to placebo, which is an acceptable ratio given the 2:1 randomization ratio. Those patients that were randomized but not dosed in the Comparative Phase, and are listed as having an adverse event that led to discontinuation (n = 3), did have an adverse event during the test-dose phase but did not discontinue from study until after they went through randomization.

Protocol Violations/Deviations

There were several protocol deviations throughout the study, but only some were deemed significant enough to warrant exclusion from the analysis. Among the mITT population (n = 201), there were 15 protocol deviations that were deemed significant enough to be excluded from the per protocol analysis. Of these, 9 patients were in the MDZ NS treatment group, and 3

subjects were in the placebo group. The other 3 subjects were randomized but did not receive a dose in the Comparative Phase.

The protocol deviations that resulted in exclusion from the primary efficacy analysis are summarized below in Table 8.

Table 8 Major Protocol Deviations Excluded from Per Protocol Analysis

Patient ID	Treatment Group	Reason for Exclusion	Deviation Category	Treatment Success Y/N
(b) (6)	USL261	Patient received an extra dose of 100 mg Tegretol on same day as IP dosing	Excluded Concomitant Treatment	N
	USL261	Patient had seizure at 9:15 am treated with 1 mg Ativan and VNS Magnet Swipe, then treated with USL261 at 17:50 on same day, within 24 hours of Ativan use.	Excluded Concomitant Treatment	Y
	USL261	Keppra administered within 6 hours of 1 st dose administration	Excluded Concomitant Treatment	Y
	USL261	Seizure at 10:20 am treated with 10 mg Valium. Then the following day at 9:11 am had 1 st dose study drug, less than 24 hours later from valium use.	Excluded Concomitant Treatment	Y
	USL261	Patient enrolled onto study on chronic benzodiazepine use	Inclusion/Exclusion Criteria	Y
	USL261 (2)	Dosed with Ativan within 24 hours of taking study drug	Excluded Concomitant Treatment	N
	USL261	Drug administered 47 min after seizure cluster began. Second dose not given when 2 nd cluster occurred 5 hours later.	Investigational Product	N
	USL261 (2)	Caregiver did not administer study drug per approved PMP	Investigational Product	N
	USL261 (2)	Patient treated with daily benzodiazepines (Clobazam)	Inclusion/Exclusion Criteria	N
	Placebo	Patient did not fulfill eligibility criteria at visit 1 but not identified until after completed study	Inclusion/Exclusion criteria	Y
	Placebo	CG did not give 1 st dose until seizure cluster almost ended	Investigational Product	Y
	Placebo (2)	Patient took clonazepam within 6 hours of IP dosing	Excluded concomitant treatment	N

Source: Adapted from Study 401 CSR Table 16.2.2, and dataset ADEF.xml

(2) received second open-label dose of USL261

Reviewer's comment: Overall, the above protocol violations were significant in that patients

were included in the mITT that met exclusion criteria (on chronic daily benzodiazepines), or received another benzodiazepine within 24 hours prior to dosing. However, the exclusion of patients currently taking benzodiazepines was more for safety reasons than efficacy reasons, as there was a concern for increased respiratory depression with excess sedating medications given concomitantly. Safety of these patients is reviewed below in Section 8.4. Overall, with the above patients removed, the primary efficacy analysis was also completed on the per protocol (PP) population. These results still demonstrate a treatment success of 54.4% in the treatment group, and 32.8% in the placebo group, with a treatment difference of 21.6%. See Table 13.

Demographic Characteristics

Overall, the two treatment groups were quite comparable regarding the demographic characteristics (Table 9).

Table 9 Demographic characteristics in the mITT population by treatment arm

Demographic Parameters	Placebo Group (N = 67) n (%)	MDZ NS Treatment (N = 134) n (%)	Total (N = 201) N (%)
Sex			
Male	30 (44.8)	68 (50.8)	98 (48.8)
Female	37 (55.2)	66 (49.2)	103 (51.2)
Age			
Mean years (SD)	31.5 (12.83)	34.0 (11.23)	33.1 (11.8)
Median (years)	27	32	32
Min, max (years)	12, 62	14, 61	12, 62
Age Group			
< 18 years	5 (7.5)	5 (3.7)	10 (5.0)
≥ 18 - < 65 years	62 (92.5)	129 (96.3)	191 (95.0)
≥ 65 years	0	0	0
Race			
White	65 (97.0)	125 (93.3)	190 (94.5)
Black or African American	1 (1.5)	3 (2.2)	4 (2.0)
Asian	0	2 (1.5)	2 (1.0)
American Indian or Alaska Native	0	2 (1.5)	2 (1.0)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (1.5)	2 (1.5)	3 (1.5)
Ethnicity			
Hispanic or Latino	4 (6.0)	10 (7.5)	14 (7.0)
Not Hispanic or Latino	63 (94.0)	124 (92.5)	187 (93.0)
Region			
United States	22 (32.8)	52 (38.8)	74 (36.8)
Rest of the World			
Australia/New Zealand	2 (3.0)	12 (9.0)	14 (7.0)
Canada	0	1 (0.8)	1 (0.5)

Western Europe	7 (10.4)	20 (14.9)	27 (13.4)
Eastern Europe	36 (53.7)	49 (36.6)	85 (42.3)

Source: Reviewer created table from Study 401 ADSL mITT population dataset

Reviewer's comment: There is a higher percentage of patients from Eastern Europe in the placebo group compared with the treatment group, which could potentially confound the results if there are regional differences seen in placebo response rates. The two treatment groups were otherwise very comparable in terms of sex, age, race, and ethnicity.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline disease characteristics were balanced, in general, between the two treatment groups (Table 10) with no significant variability in seizure history, seizure type, or frequency/severity of seizure clusters. There were no key features of the medical history that varied significantly among the two populations.

Table 10 Seizure Cluster History in the mITT population

Parameter	Placebo (N = 67)	USL 261 (N = 134)	Total (N = 201)
Typical Cluster Duration (minutes)			
n	63	129	192
Mean	239.34	270.77	260.46
Median	60	65	65
# years pt has had seizure clusters			
n	64	133	197
Mean	6.69 (6.3)	9.88 (10.11)	8.84 (9.16)
Median	5	5	5
# clusters in past 1 year before Visit 1			
n	67	134	201
Median	15	18	18
# seizures in each cluster episode			
n	67	134	201
Mean (SD)	14.16 (25.57)	12.81 (23.60)	13.26 (24.22)
Median	6.00	5.25	6.00
Min, Max	2, 170	2, 200	2, 200
Seizure type in cluster, n (%)			
Simple partial seizure	17 (25.4)	23 (17.2)	40 (19.9)
Complex partial seizure	33 (49.3)	71 (53.0)	104 (51.7)
Secondarily generalized tonic clonic convulsion	20 (29.9)	46 (34.3)	66 (32.8)
Primary generalized tonic clonic convulsion	7 (10.4)	8 (6.0)	15 (7.5)
Tonic	3 (4.5)	8 (6.0)	11 (5.5)
Atonic	0	2 (1.5)	2 (1.0)
Other	3 (4.5)	17 (12.7)	20 (10.0)

Source: Adapted from Study 401 CSR Table 14.1.4.4.2 (reviewer verified in JMP)

Patients were also characterized as to whether they were "AED-induced" (Table 11). The

following enzyme-inducing AEDs were included: carbamazepine, clobazam, eslicarbazepine, ehotoin, felbamate, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide, topiramate. If any of the above medications were used within the SAP-specified 14-day window before administration of the blinded study drug, then the patients were considered AED-induced.

Reviewer's comment: The number of patients considered "AED-induced" in the MDZ NS group (61.9%) was slightly higher than the number of patients considered "AED-induced" in the Placebo group (49.3%). Given that it is possible that the patients who are "AED-induced" would have lower exposures of study drug because of increased metabolism, it is significant that there was still treatment success in the MDZ NS group, despite slightly more patients who were enzyme-induced.

Table 11 AED Enzyme Induction Status in the mITT population

Category	Placebo (N = 67)	USL 261 (N = 134)	Total (N = 201)
Any enzyme-inducing AEDs	34 (50.7)	87 (64.9)	121 (60.2)
No enzyme-inducing AEDs	33 (49.3)	47 (35.1)	80 (39.8)
Considered AED-induced	33 (49.3)	83 (61.9)	116 (57.7)

Source: Study 401 CSR 14.1. 10.4.3, verified in JMP

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In terms of concomitant medications, all patients were on a significant number of other AEDs. There was no significant difference in benzodiazepine use between the placebo and USL261 populations, although the specific benzodiazepine was different. As seizure medication, 38% of MDZ NS and 34% of placebo group used benzodiazepines or derivatives. Of note, 50% of those patients that received a test dose, but were not randomized, used as needed benzodiazepine or derivatives, so ability of a patient to tolerate the test dose was not dependent on the patient having prior benzodiazepine use or being "benzodiazepine-naïve".

Treatment compliance was not a concern for this acute treatment, single dose, study. Rescue medications were individualized per each patient's PMP, which were finalized and reviewed prior to randomization.

Efficacy Results – Primary Endpoint

Treatment success was demonstrated on the primary efficacy endpoint in the mITT population, as per the pre-specified planned statistical analysis (Table 12).

Table 12 Treatment Success (mITT population)

Treatment success	Placebo N = 67	MDZ NS N = 134
n (%)	23 (34.3)	72 (53.7)
95% CI	(23.0, 45.7)	(45.3, 62.2)
MDZ NS-Placebo Treatment Difference	19.4%	
1-sided p-value from Fisher's exact test		0.0069
2-sided p-value from Fisher's exact test		0.0109
p-value from chi-square test		0.0094

Source: Study 401 CSR Table 14.2.1.1.1 (reviewer verified in JMP)

In her biometrics review, Dr. Xiang Ling also verified the findings of the applicant. As noted, the 1-sided p-value for the primary analysis from Fisher's exact test was 0.0069, which is smaller than the proposed statistical significance level of 0.0085 (1-sided) for the final analysis, suggesting that the treatment difference noted is statistically significant.

Reviewer's comment: As noted in Dr. Ling's review, the applicant's proposal of using a significance level of 0.0085 was reasonable in this situation. Had the study been planned with a sample size of 201, and with only two interim analyses as actually performed, the alpha left for the final analysis would be 0.013. However, unplanned changes should generally be avoided after unblinded analyses have been conducted. And based on the SAP prior to the first interim analysis, a 1-sided p-value < 0.0085 for the analysis with n = 201 (planned n = 204) would cross the Pocock boundary either as the 3rd interim analysis or as the final analysis.

Please see Dr. Ling's Biometrics Review for further detail on the appropriateness of the statistical analysis, and the verification provided by the Chi-Square test (with a 2-side alpha level of 0.017) given the increased sample size.

Sensitivity Analysis of subgroup populations

As noted in the biometrics review, the analyses conducted with baseline covariate adjustment for subgroups analysis support the robustness of the primary analysis. The analysis by age group (Cochran-Mantel-Haenszel) test, and the exploratory logistic regression model with backward selection of covariates both indicated that the proportion of patients with treatment success was greater in the treatment arm compared with the placebo arm. The analyzed covariates were age, sex, BMI, geographic region and AED-inducer status.

Reviewer's comment: There were no statistically significant differences in treatment effect by subgroup analysis as noted above. However, this reviewer did note that there is a slightly higher treatment difference in Eastern Europe compared to North America/Australia and Western Europe. This treatment effect seems to be driven by a slightly lower than average placebo response rate, and there was a higher percentage of placebo patients in Eastern Europe, see Table 9 above. However, small numbers make this difficult to interpret.

Also, a treatment difference was noted to be somewhat diminished in obese patients (-2.5) which may be because of under-dosing in those that are obese. The small number of patients makes that finding hard to interpret.

This reviewer also examined the results of the treatment success in the per protocol population (PPP) after removal of those with major protocol deviations (Table 13). Given a significance level (2-sided) of 0.017, the treatment difference is still shown to be statistically significant.

Table 13 Sensitivity analysis for Treatment Success (Per Protocol Population)

Treatment success	Placebo N = 64	MDZ NS N = 125
n (%)	21 (32.8)	68 (54.4)
95% CI	(21.3, 44.3)	(45.7, 63.1)
USL-261-Placebo Treatment Difference	21.6%	
2-sided p-value from Fisher's exact test		0.0056
p-value from chi-square test		0.0049

Source: Study 401 CSR Table 14.2.1.1.2, reviewer verified in JMP

The applicant also provided an analysis of the components of treatment success, which this reviewer verified (Table 14).

Table 14 Treatment Success Components

	Placebo N = 67	MDZ NS N = 134
Component of treatment success for all patients		
Termination of seizure within 10 minutes		
Yes, n (%)	47 (70.1)	108 (80.6)
No, n (%)	20 (29.9)	26 (19.4)
No recurrence of seizure with start time > 10 minutes and ≤ 6 hours		
Yes, n (%)	38 (56.7)	90 (67.2)
No, n (%)	29 (43.3)	44 (32.8)
No second dose within 6 hours of study drug		
Yes, n (%)	26 (38.8)	92 (68.7)
No, n (%)	41 (61.2)	42 (31.3)

Source: Study 401 CSR Table 14.2.1.2, reviewer verified in JMP

Reviewer's comment: Seizure clusters are, by definition, episodes of brief, repetitive seizures. Therefore, it follows that a high percentage of patients who received placebo (70%) had termination of seizures within 10 minutes, and why seizure termination alone would not have been a reasonable endpoint for the study. However, it is still important that an even higher percentage of patients in the MDZ NS treatment group had seizure termination within the same ten minutes following drug administration. A higher percentage of patients who received placebo had seizure recurrence (43%) compared to the MDZ NS treatment group (33%), and an even higher percentage of patients in the placebo group required a second dose

(61%) compared to the MDZ NS treatment group (31%). Taken together, these components are supportive of the clinical meaningfulness of the treatment effect.

Data Quality and Integrity

OSI completed inspections of four clinical sites in support of this NDA. Please see Clinical Inspection Report by Cara Alfaro for details. The overall assessment was that the studies were conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. There was one site (Site #70, Dr. Fakhoury, Lexington, Kentucky, US) that had regulatory violations identified. A screening ECG to determine subject eligibility was not performed for one enrolled subject, and protocol-required ECGs for this same subject were not performed during the test-dose phase. The patient was developmentally delayed and could not comply with the ECG, but the investigator did not note the missing ECG until after patient had completed the study. It was not felt that these missing ECGs would affect the overall safety analysis, and the site was classified as Voluntary Action Indicated.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoints no longer have the full alpha of 0.05 (2- sided) because of the interim analyses conducted. Our statistical team agreed with the applicant's conservative approach of using the same alpha level of 0.017 (2-sided) that was specified for the primary endpoint, as the SAP did not clearly specify the alpha level of the secondary endpoints.

The secondary endpoint results were dependent on whether the initial seizure terminated after double-blind study drug administration, and when it terminated. Therefore, the results of the secondary endpoints could not be interpreted independent of the result for the treatment effect on the initial seizure. For example, if a patient's seizure did not terminate, or stopped much later, then it would be register as a "positive" result of the secondary endpoints, which measured time to next seizure and recurrence of seizure within 4 hours. Furthermore, because both key secondary endpoints rely on "next seizure", but all patients did not have a second seizures, the results are biased with loss of randomization.

- Time to next seizure with start time > 10 minutes after double-blind study drug administration

For this analysis, patients administered a second dose of study drug and not having a seizure before the administration of the second dose were censored at the time of the second dose. See

Table 15 for details of the analyses provided by the applicant and conducted by Dr. Ling. Dr. Ling also conducted her own review of the time to next seizure, assuming that all patients who received a second dose within 24 hours were assumed to have a seizure, which also supported the treatment effect on time to next seizure within 24 hours (Table 16).

Table 15 Time to Next Seizure with a Start Time at Least 10 minutes after Study Drug Administration

	Placebo N = 67	MDZ NS N = 134
Occurrence of next seizure within 24 hours; n (%)	31 (46.3)	50 (37.3)
Median Time (hours) to next seizure	12.1	
Probability of having next seizure in 24 hours (%) ^a	62.9	41.7
p-value ^a	0.0124	
Hazard Ratio (MDZ NS: Placebo) (95% CI) ^b	0.57 (0.36, 0.89) p = 0.0138	

Source: Study 401 CSR Table 14.2.2.1.1 and Dr. Ling's Biometrics Review

^a Based on log-rank test; statistically significant at level 0.017

^b Based on Cox model including treatment as the independent variables; statistically significant at level 0.017

Table 16 Time to Next Seizure with a Start Time at Least 10 Minutes after Double-Blind Study Drug Administration (Statistical Reviewer analysis)

	Placebo N = 67	MDZ NS N = 134
Occurrence of next seizure within 24 hours; n (%)	50 (74.6)	66 (49.3)
Median Time (hours) to next seizure	1.3	
p-value ^a	0.0001	
Hazard Ratio (MDZ NS: Placebo) (95% CI) ^b	0.50 (0.34, 0.72) p = 0.0002	

Source: Dr. Ling's Biometrics Review

^a Based on log-rank test; statistically significant at level 0.017

^b Based on Cox model including treatment as the independent variables; statistically significant at level 0.017

Reviewer's note: The median time to next seizure is significantly shorter in the second analysis because many patients may have received a second dose of study drug not for a seizure recurrence but because the original seizure did not terminate. Therefore, by utilizing the time the second dose was given as a surrogate for time of next seizure, the median time to next seizure is significantly shortened. However, both analyses are supportive of a treatment effect and demonstrate that the treatment does significantly reduce the time to next seizure.

- Recurrence of Seizure Beginning 10 min after Administration of Double-Blind Study Drug to 4 hours After Study Drug Administration

For this analysis, the patients who received the second dose of study drug within 4 hours of double-blind study drug administration were assumed to have had a recurrence of seizure (Table 17).

Table 17 Recurrence of Seizure(s) from 10 Minutes to 4 hours After Double-Blind Study Drug Administration

	Placebo N = 67	MDZ NS N = 134
Recurrence of Seizure		
n (%)	40 (59.7)	51 (38.1)
95% CI	(48.0, 71.4)	(29.8, 46.3)
p-value from Fisher's Exact test	0.0043	
p-value from Chi-square test	0.0037	

Source: Study 401 CSR Table 14.2.2.1, verified in JMP

Dose/Dose Response

Not applicable.

Durability of Response

Not applicable for this study design, and the proposed acute, intermittent use of the product.

Persistence of Effect

Not applicable for this single dose study design.

Additional Analyses Conducted on the Individual Trial

- Exploratory Endpoints - Subject and Caregiver Outcome Assessments

The applicant provided analysis of the caregiver and patient-reported SF-12v2 on quality of life, which demonstrated no significant differences in any domains for within-group comparisons of change from baseline or for MDZ NS compared to placebo.

The analysis of the treatment satisfaction questionnaire for medication (TSQM), which was measured at visit 4, demonstrated significant improvement in MDZ NS group compared with placebo for the domains of effectiveness and convenience ($P < 0.0001$ and $p = 0.0238$, respectively, using paired t-test method).

- Efficacy of Second Dose

This reviewer also conducted an analysis of the treatment effect of the second dose. However, no statistical analyses could be adequately conducted because of lack of blinding of the second dose, and the confounding nature of giving the open-label treatment dose to patients who had previously received placebo.

Table 18 Treatment Success of Second Dose of Study Drug

Parameter	Placebo N = 67	MDZ NS N = 134
Received second dose within 6 hours; n (%)	41 (61.2)	42 (31.3)
Treatment success of the second dose ^a		
n (%)	27 (65.9)	23 (54.8)
95% CI	(51.3, 80.4)	(39.7, 69.8)
Component of Treatment success for all patients		
Termination of seizure(s) within 10 minutes ^b		
n (%)	38 (92.7)	34 (81.0)
95% CI	(84.7, 100.0)	(69.1, 92.8)
No recurrence of seizure(s) with start time > 10 minutes and ≤ 6 hours ^b		
n (%)	29 (70.7)	31 (73.8)
95% CI	(56.8, 84.7)	(60.5, 87.1)

Source: Study 401 CSR Table 14.2.3.3.1, reviewer verified in JMP

^a Treatment success of second dose was defined as achieving both termination of seizure(s) within 10 minutes and no recurrence of seizure(s) with a start time > 10 minutes and ≤ 6 hours following the second dose.

^b This analysis only includes patients who received the second dose of the study drug.

Within the MDZ NS treatment group, there were 42 patients who did not respond to the first dose of treatment and received a second 5 mg dose MDZ NS. Of the 42 who received a second dose, 23 (54.8%) responded to the second dose. Among those patients who received placebo in the double-blind treatment phase, 41 patients received a 5 mg MDZ NS dose for continued or recurrent seizure activity. Of these 41 patients, 27 (65.9%) met treatment success criteria.

The time at which the second dose were given were as follows:

Time of second dose (after double blind study drug administration)	Placebo Arm N = 41		MDZ NS Arm N = 42	
	n	Treatment success n (%)	n	Treatment Success n (%)
< 10 minutes	1	1 (100)	0	n/a
> 10 minutes to < 20 minutes	25	16 (64)	17	12 (71)
> 20 minutes to < 1 hour	6	3 (50)	6	3 (50)
> 1 hour to < 6 hours	9	7 (78)	19	8 (42)
> 6 hours	0	n/a	1	1 (100)

Source: Reviewer analysis of Study 401 ADEF dataset

Reviewer's comment: It is difficult to derive any evidence of effectiveness of the second dose from the data available, especially given any lack of blinding or re-randomization between the first dose and the second dose. However, the data does add some supportive evidence to the effectiveness of the study treatment, as there was a high percentage of treatment success (65.9%) in patients who received the treatment after initially receiving placebo. These patients who have likely been more "refractory" as they had been having the cluster/seizure for longer; however, the even higher percentage of treatment success in those who received the second dose at a later time period (> 1 hour to < 6 hours) may also demonstrate the

natural history of some of the clusters to stop on their own. That is why the data are not compelling without a true comparator arm.

There were no major baseline or disease characteristics that indicated which patients responded to second dose, in terms of sex, weight, BMI, region, or enzyme-inducers, etc. Of the 19 patients who did not respond after the second dose of MDZ NS, 16/19 had enzyme inducing status. Unclear if this is significant at all regarding dose in these patients, or potentially indicating that these patients may benefit from a higher dose because of enzyme-inducing status. The small sample size precludes drawing any conclusions regarding dose and enzyme-inducing status.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

There is only a single efficacy study included in this review and therefore this section is not applicable.

7.1.1. Primary Endpoints

There is only a single efficacy study included in this review.

7.1.2. Secondary and Other Endpoints

There is only a single efficacy study included in this review.

7.1.3. Subpopulations

There is only a single efficacy study included in this review.

7.1.4. Dose and Dose-Response

There is only a single efficacy study included in this review.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

There is only a single efficacy study included in this review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Intranasal midazolam may allow early effective treatment of seizures in other situations beyond outpatient treatment of seizure clusters, especially in inpatient hospital settings, emergency rooms, or EMS environments when IV access has been lost or is not rapidly available. There are also potential implications for use of intranasal midazolam in prolonged seizures or in early status epilepticus by emergency room and EMS personnel, or even in the outpatient setting by caretakers.

Given the recent approval of Seizalam (IM MDZ) for the treatment of status epilepticus, it is reasonable to expect future studies of the benefit of MDZ NS in status epilepticus as well, as intranasal administration may have widespread appeal not just over rectal alternatives, but also over IM/IV alternatives.

There were only a few adolescents in the study, but no indications that efficacy or PK would vary in those patients down to age 12 years. Pediatric patients under 12 years of age have not been studied and therefore will not be included in the indication/labeling. Consideration for future pediatric studies is needed, even though this application does not trigger PREA as it is an orphan designation. Off-label use of MDZ NS in pediatric patients is expected because of the convenience of administration, and should therefore ideally be further studied to determine efficacious doses in younger patients.

Overall, the population studies in this study should be similar to the US population, and would presumably have similar efficacy in the postmarket setting for the proposed indication. However, the off-label use would probably be expanded to include additional patient populations and seizure types, as well as patients with multiple other comorbid conditions, so other safety considerations may be required (see Section 8.9.2).

7.2.2. Other Relevant Benefits

When compared to the only approved alternative treatment of diazepam rectal gel, there are many relevant benefits to the patient and caregiver regarding ease of administration, patient compliance and cooperation, and ability to use in public settings (i.e., school, workplace, supermarket).

7.3. Integrated Assessment of Effectiveness

Overall, as noted in Section 3, a single, pivotal trial with a robust positive outcome may be sufficient for demonstrating evidence of effectiveness. The above-described efficacy analysis from Study 401, demonstrating statistical significance on the primary and key secondary endpoints, therefore meets the statutory evidentiary standard. The benefit noted on both termination of seizures within 10 minutes, and prevention of future seizures in a cluster for a

minimum of 6 hours, and up to 24 hours, is very clinically meaningful, as seizure clusters have a risk for evolving into prolonged seizures and/or status epilepticus. A medication that can be given at home, by a caregiver, and stop further seizures is likely to greatly reduce not only complications from seizure clusters, but also significant reduction in ER visits and hospitalizations, which would also be clinically meaningful.

There is also further supportive evidence from two supportive studies and the literature, which, although limited in their interpretability, are briefly discussed here. These data are not required to support the approval of Nayzilam; however, they provide additional assurance of the consistency of the results observed in Study 401.

Study P261-402

Study 402 was an open-label extension for patients who completed Study 401, so the ability to study efficacy is difficult given the open-label nature of the study. However, the applicant evaluated all patients receiving the study drug for treatment success, using the same criteria for the primary endpoint from Study 401, which was termination of seizure within 10 minutes and no recurrence of seizures within 10 minutes and < 6 hours after study drug dose. The patients all used the same subject workbook, and followed their individual PMP from Study 401.

Patients were given a single 5 mg MDZ NS dose for each seizure cluster, with an option to give a 2nd dose after 10 minutes if they met the 2nd dose eligibility criteria. A minimum of 3 days was required between study drug treatments, but no limitation on the total number of seizure cluster episodes was given. Patients initially returned for visits after a treated seizure cluster for the first two clusters, then they subsequently returned for visits after every two treated seizure clusters, and within 5 days of the last dose of MDZ NS.

The efficacy analyses were all descriptive, with no primary efficacy variable identified, and no hypothesis tests. However, 175 patients met the eligibility criteria and enrolled in Study 402, and 161 patients received at least 1 dose of study drug in the study and had a post-treatment efficacy assessment. No patients were lost to follow up, and the study was terminated when Study 401 was terminated, in January 2017 for business reasons.

Overall, the 161 patients treated 1,998 seizure clusters, with a mean of 12.4 clusters per patient, over 18.8 months. There were 1,108 clusters (55.5%) that met the criteria for treatment success after the first dose. For each patient, the mean percentage of treated clusters meeting success was similar at 54%. There were 35% of patients who had seizure recurrence in the 4 hours after receiving study-drug, similar to the numbers in Study 401. There was no apparent tachyphylaxis or need for escalating doses or tolerance to study drug as the study went on after chronic, intermittent use of the drug. The overall proportion of treated seizure clusters successfully treated did not diminish with later episodes.

A second dose was administered in 797 (39.9%) of treated seizure clusters. The mean time

between the two doses was 2.33 hours, with 33% of the treated clusters (264) being treated with the second dose within 20 minutes of the initial dose, and 25% (206) receiving the second dose within 2-4 hours. A total of 109 patients used 10 mg dose for at least some of their seizure clusters, and these patients had a mean of 14.9 seizure clusters each, and used the 10 mg dose for a mean of 7.3 clusters, so patients did not use or require a second dose for every cluster. They did not require increased use of 10 mg dose over time.

Overall, 86.3% of treated clusters met criteria for treatment success after first or second dose, with a median time to return to full baseline of 1.2 hours, and 74% returned to full function within 24 hours.

Reviewer's comment: Although there is little statistical analysis of the open-label extension trial, the patients and their caregivers administered treatment and recorded treatment response in a similar way as they did in the pivotal Study 401. The response rates were similar to those seen in the double-blind treatment period, with treatment success in about 55% of treated seizure clusters after the first dose, and more importantly, no evidence of waning response over time.

(b) (4)

Published literature

The applicant provides references for a few trials demonstrating use of intranasal midazolam (in other formulations) in similar patient populations that are supportive of the chosen dose and efficacy of midazolam in the treatment of seizures. The studies are of limited interpretability given publication bias and lack of available datasets for review, but do provide some supportive information and are reassuring that similar doses to those used in Study 401 have been used previously with apparently consistent efficacy results.

Overall, the body of literature revealed 24 studies that were randomized, controlled clinical studies (some blinded, some non-blinded) utilizing midazolam via intranasal, buccal, intramuscular, and intravenous routes for variable acute seizure emergencies. There were 5 additional meta-analyses in the literature for the use of MDZ in status epilepticus. All the studies found MDZ effective in the treatment of acute seizures, with seizure cessation ranging from 56-100%, and was as effective as or superior to, active comparators (diazepam (DZP), or lorazepam (LZP)). In the literature, the intranasal, buccal, and IM routes of administration had overall times from arrival to seizure cessation that were faster or similar to rectal/IV administration because of rapidity and ease of use. Meta-analyses demonstrated that non-IV MDZ was effective for status epilepticus, and a valid "alternative" to LZP and DZP.

The published literature also evaluated the off-label use of the parenteral formulation in prefilled syringes for either intranasal or buccal administration, which is prone to inaccurate dosing and administration mistakes. In some of the studies caregivers also used a multi-dose vial and measured and administered a dose with a separately packaged atomizer, which is similarly prone to dosing and administration error. The intranasal route utilizes nasal mucosa for absorption, avoiding the first-pass metabolism. The literature described 9 randomized, controlled studies of 520 patients comparing IN MDZ to either IV or rectal DZP. Each study concluded that IN MDZ was as effective as, or superior to, DZP, with overall cessation rates of 67-100% and unique advantages of the IN route of administration. IN MDZ, without the first-pass metabolism and lack of need for IV placement, controlled seizures more rapidly than the IV and rectal DZP routes. IN and buccal MDZ also showed similar efficacy for control of early status epilepticus in the literature.

Reviewer's comment: Although there was limited interpretability of the data in the published

literature, it does provide a large body of evidence that illustrates the widespread use of midazolam in the acute treatment of various seizure types, as well as the accepted use of intranasal midazolam in various formulations, and the relative benefits compared to other approved therapies (noting the many limitations of such comparisons based on these data).

8. Review of Safety

8.1. Safety Review Approach

The main portion of the safety review will come from Study 401, the randomized, controlled pivotal study with analyses of both the open-label Test Dose phase and the double-blind Comparative Phase. The safety review will also include a summary of adverse events that were notable in the open-label extension trials (Study 402 and Study 408), as well as patients from the randomized, controlled Study 301 (see Section 5.1 Table of Clinical Studies). The patients in Study 301 represent a different patient population than the proposed indication, as the patients were admitted to the hospital Epilepsy Monitoring Unit (EMU) for work-up of refractory epilepsy, and they did not have a diagnosis of seizure clusters. Because of the inevitable differences in baseline disease characteristics, as well as the treatment in a monitored inpatient setting vs the proposed outpatient community setting, it (b) (4)

However, data from Study 301 is reviewed below.

Furthermore, MDZ is an approved treatment and has a well-characterized safety profile, but has not been approved for treatment of acute repetitive seizures, and has never been approved for intranasal administration. Although the recent approval of Seizalam characterized a safety profile of MDZ for the treatment of status epilepticus, the severity of the treated condition and the difference in treatment administration (caregiver vs EMS provider), render the data from Seizalam not applicable. However, as noted above, there is a significant body of literature that explores the use and safety of midazolam in the treatment of seizure clusters/acute repetitive seizures. Thus, the safety of MDZ NS is primarily focused on the known potential risks for respiratory depression or other CNS-depressant-related adverse events, as well as the potential for local nasal toxicity and olfactory toxicity.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Although the safety review will focus on the patients in Study 401, the complete safety population includes all patients who received 1 or 2 doses of 5 mg MDZ NS in the Phase 3 studies, including Study 401, 402, 408, and 301 (See Section 5.1). A total of 361 patients received treatment in the Phase 3 studies, and a total of 232 were randomized and treated in

the double-blind, controlled phase of the studies. There was a total of 627 patients and healthy subjects were exposed to at least one dose of MDZ NS if all Phase 1 studies are included as well in the safety population.

Table 19 Table of Exposure Durations and Clusters Treated in Study 402 characterizes the long-term safety data collected in the open-label extension Study 402 in terms of duration of treatment, and number of total clusters treated per patient and per patient per year.

Table 19 Table of Exposure Durations and Clusters Treated in Study 402

Dosage	Number of patients exposed to the study drug:				
	≥ 1 dose	0 to ≤ 6 months	≥ 6 to < 12 months	≥ 12 months to < 24 months	24 months or longer
Any dose MDZ NS (N)	161	19	36	63	43
	Number of Total Clusters Treated Per Patient				
	1-5 clusters	6-15 clusters	16-30 clusters	31-50 clusters	> 50 clusters
5 or 10 mg MDZ NS (N)	66	53	27	9	6
	Number of Clusters Treated Per Patient Per Year				
	< 2 / year	2 to < 4/year	4 to < 12/ year	12 to < 26/ year	26 to < 52/ year
5 or 10 mg MDZ NS (N)	25	27	77	29	3

Source: Reviewer's analysis of Study 402 ADSL dataset

Reviewer's comment: In early correspondence with the applicant after the End of Phase 2 Meeting in 2013, and in a Type C meeting in 2015, the Division agreed with the applicant's proposal for a minimum exposures of at least 470 subjects (patients and healthy subjects) exposed to at least one dose of 5 mg MDZ NS, and a minimum of 132 patients with multiple exposures to treat > 1 seizure episodes, including ≥ 50 patients with chronic, intermittent treatment over a 1-year period, and at least 20 patients with at least 5 acute seizure episodes requiring treatment. The applicant has met these numbers. At the same time, (See Section 3.2) the Division also requested a review of literature of nasal and olfactory toxicity for intranasal MDZ, and the addition of the B-SIT for testing of olfactory toxicity.

In the open-label extension Study 402, I also examined the frequency of the treatments that was studied for further recommendations on treatment frequency for labeling. There were 214 treated seizure clusters in 61 patients that were treated less than 7 days apart. There were 68 patients who treated 384 clusters with 7-14 days between clusters. And there were 96 patients who treated 578 clusters with 14-30 days between them. All other clusters were > 30 days apart.

Further, of the 214 treated clusters less than 7 days apart, there were 57 clusters treated ≤ 3 days apart, and 60 clusters treated >3 and ≤ 5 days apart, and 97 clusters that were >5 and ≤ 7 days apart. Among these patients that treated clusters close together, that do not appear to be any patients who treated more than 4 to 5 clusters in a month.

Reviewer's comment: Although patients were allowed to treat after a minimum of 3 days, it appears that most patients treated clusters on a weekly, biweekly, or monthly basis. It is hard to determine the maximum monthly dose that would be tolerated. However, there did not seem to be any unique safety signals in those patients who did use the drug either weekly or almost 50+ times in a year. To avoid dependence and abuse, use more than every 3 days is not recommended.

Given that the safety of treating more than 5 seizure clusters in a month is unknown, and there should be no presumption that it is safer than the recommended instructions for use of Diastat, which is recommended to treat no more than 5 episodes in a month, I recommend keeping that proposed language in the prescribing information.

8.2.2. Relevant characteristics of the safety population:

The key safety analyses were performed on the safety population from pivotal Study 401 and its long-term extension Study 402. The demographics and baseline disease characteristics of this population are reviewed in Section 6.1.2. The additional patients from the other Phase 3 studies (Study 301 and Study 408) are included in some analyses below for supportive data, and do not vary significantly from the Study 401 population except as noted above.

8.2.3. Adequacy of the safety database:

In Study 401, there were a total of 292 patients who received two 5 mg MDZ NS doses of study drug in the Test Dose phase (open-label), separated by 10 minutes. Of those, 201 patients went on to be treated in the double-blind Comparative Phase, randomized 2:1 MDZ NS: placebo, with 134 patients randomized to MDZ NS and 67 patients randomized to placebo. Patients were then given an optional open-label treatment of 5 mg MDZ NS after 10 minutes for refractory or recurrent seizure activity. Therefore, out of 201 patients in the Comparative Phase, 67 randomized to placebo and of those, 26 patients received placebo only, and 41 patients received placebo initially followed by 5 mg MDZ NS. Of the 134 patients randomized to MDZ NS, 91 patients received only 5 mg MDZ NS, and 42 patients received 10 mg MDZ NS, separated from 10 minutes to up to 6 hours.

In the long-term extension study, Study 402, there were 175 patients enrolled, and 161 patients treated a seizure cluster with study drug. The mean was 12.4 clusters per patient, with a median of 7 clusters treated per patient. A total of 109 patients used the 10 mg dose (2 separate 5 mg MDZ NS doses). While these 109 patients had a mean 14.9 clusters per patient, with a median of 9 clusters per patient, the higher dose was only used on a mean of 7.3 clusters. Only 23 patients used 10 mg for every single one of their treated clusters, and those patients had a mean of 4.8 clusters.

Reviewer's comment: The treatment in the test dose phase of Study 401, which consisted of 2 doses of 5 mg MDZ NS, 10 minutes apart, is significant for the safety review for a few reasons. Although the interpretability of these uncontrolled data is limited because of the open-label nature of the phase and lack of comparator, it is the highest dose that will be included in the proposed usage section (and separated by the shortest duration of only 10 minutes), and may therefore help to identify risk factors for those patients who could not tolerate the dose, or should not receive the drug in the outpatient setting. However, I note that the test-dose was given to patients in a non-seizure setting, which may inherently change the nature of the AEs that are noticed and recorded by patient and caregiver, and may over-estimate the risk for some AEs in the patient population. For example, certain AEs may not have been noted by a patient who was post-ictal or in the midst of a seizure, or would not have been deemed significant, but in the absence of a seizure may seem more worrisome (e.g., sedation, dizziness, etc.).

Finally, although this will be discussed in more detail below, patients with significant adverse events in the test dose phase were not allowed, by protocol, in to the Comparative Phase. If there was any indication of a high-risk population that should use caution with using the drug in an outpatient setting, they would have only been captured in this open-label Test Dose phase, as they would have been excluded before randomization.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no concerns regarding the integrity of the data submitted for the safety review. The datasets provided by the applicant were complete and not-misleading, and I was able to sufficiently reproduce the safety analyses of the applicant, and perform my own analyses when necessary.

8.3.2. Categorization of Adverse Events

Treatment Emergent Adverse Events (TEAE)

A TEAE in the Test Dose Phase was defined as new or worsened adverse event (AE) with onset on or after study drug administration at Visit 2 and up to the first dose of study drug in Comparative Phase, or end of study. A TEAE in the Comparative Phase was defined as a new or worsened AE with onset on or after first dose of study drug in Comparative Phase. A worsened AE was compared to the same event occurring prior to the test dose. The applicant also consider the following AEs as treatment-emergent:

- AE with the same onset date as the study drug start date, unless the AE start time was prior to study drug start time.
- AE with an incomplete onset date, unless there was evidence that confirmed otherwise.

- AE with completely missing start date, if the stop date was present and was after the date of first dose of study drug.

TEAEs of Special Interest (AESI)

The categories for AESI were defined in the integrated summary of safety Statistical Analysis Plan and include the following categories:

- Taste and smell disorders
- Acute central respiratory depression
- Route of administration
- Depression and suicidality/Self-injury
- Abuse-related AEs

Serious Adverse Events (SAE)

SAEs were defined as per FDA Title 21 CFR Part 312 and ICG guidelines, as any adverse event that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Causes a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Of note, an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above should also be considered serious.

AE verbatim text was coded using MedDRA coding dictionary, version 16.1, and summarized by System Organ Class and preferred term (PT). Investigators evaluated AEs for onset date, stop date, and intensity, as well as frequency, outcome, and action taken. Intensity was defined as

- 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.

Reviewer's comment: Given the prior approval of midazolam, as well as literature supporting the use of midazolam for treatment of seizures, and the well-characterized AE profile for benzodiazepines and MDZ itself, the safety plan was considered both appropriate and adequate.

Other Safety assessments that were included other than monitoring for AEs included physical, neurologic, and nasal examinations, as well as various assessments described below:

- Observer's Assessment of Alertness/Sedation Scale (OAA/S)

The OAA/S is a validated qualitative categorical measure of sedation using 4 assessment categories of responsiveness, speech, facial expression and eyes. The OAA/S is scored in 2 ways, as a Composite score (ranging from 1 (deep sleep) to 5 (alert)), for which the applicant analyzed the lowest level checked by study center personnel during Test Dose Phase, and Sum Score, or sum of the 4 assessments. The scores were used to determine pharmacodynamic parameters.

- **Columbia-Suicide Severity Rating Scale (C-SSRS)**
The C-SSRS was collected referencing 2 time points for suicidal ideation (lifetime, past 6 months) and 2 time points for suicidal behavior (lifetime, past 5 years) for baseline. For all subsequent visits a "since last visit" version was administered. Suicidal ideation was scored 1 (wish to be dead) to 5 (active suicidal ideation with specific plan and intent). Suicidal behaviors were summarized by each visit by treatment group.
- **Brief Smell Identification Test (B-SIT)**
The B-SIT was given to US only patients with baseline values defined as Visit 2, pre-dose values. The change from baseline for the 2 treatment groups was compared using a 2-sample t-test at each post-baseline time point.

For my own safety analyses of Study 401, some AE codes were recoded for ease of review and to avoid underestimating prevalence of a specific adverse event, or class of adverse event. The following table shows the original AE code on the left, and the revised codes on the right (Table 20).

Table 20 Recoded AE codes to Group Similar Terms

Original Coded Terms	Recoded Term
Bradypnea	Respiratory Rate decreased
Eye irritation, eye pain, eye pruritus, ocular discomfort	Eye irritation or pain
Convulsion, Seizure cluster	Seizure
Intranasal paresthesia, intranasal anesthesia	Intranasal paresthesia
Lethargy, malaise, fatigue	Lethargy/Malaise/Fatigue
Migraine	Headache
Oropharyngeal discomfort	Oropharyngeal pain
Rhinalgia	Nasal discomfort
Increased upper airway secretion, Salivary hypersecretion	Increased secretions

Furthermore, I reviewed all of the TEAEs that occurred during the study, and then focused much of my review on those TEAEs that occurred within 2 days of dosing. Given the acute nature of treatment, and the short half-life of the drug, it was my impression that those TEAEs that occurred beyond 48 hours after the drug administration are less likely to be drug-related and more related to the patient's underlying epilepsy or other etiologies outside of the scope of this review. All the TEAEs that were consistent with the relatively known safety profile of midazolam occurred very shortly after drug administration. Therefore, the safety tables below are focused mainly on TEAEs only that occurred in the immediate 48 hours following study drug

administration, except as noted.

I also analyzed not only the TEAEs in the double-blind Comparative Phase, but also the TEAEs in the Test Dose phase, as patients who had significant AEs after the Test Dose, even though open-label, were excluded from participating in the Comparative Phase, and thus may be significant for identification of any risk factors for medication intolerance.

8.3.3. Routine Clinical Tests

Refer to Table 3 Schedule of Key Study Procedures for a summary of the performed clinical examinations. Routine clinical tests were not performed during the Comparative Phase because of treatment being given in the outpatient community setting trial.

In the Test Dose Phase, there were routine laboratory tests, urinalysis, chemistries, and BP and ECG monitoring done. Physical exams, neurologic exams, and nasal examinations were performed at the regular Visits throughout the study.

8.4. Safety Results

8.4.1. Deaths

There were no deaths that occurred during drug development in any study.

8.4.2. Serious Adverse Events

In the Comparative Phase of Study 401, there were 2 SAEs in 2 subjects, which are outlined below. Neither SAE resulted in discontinuation from the study. Only the first event occurred within 48 hours after receiving the study drug.

- (b) (6), 56-year-old male patient, randomized to placebo, was treated with placebo and then received the open-label 5 mg active MDZ NS dose, had an event of "seizure cluster" that required a hospital visit for continued seizure activity at the same time as the treated seizure cluster.
- (b) (6), 31-year-old male patient, randomized to MDZ NS, had an SAE of "partial seizures with generalization" that occurred three days after study drug administration, and was similar to patient's baseline clusters.

Reviewer's comment: Both SAEs in the Comparative Phase are more closely related to the patient's underlying epilepsy and history of seizure clusters, and unlikely related to the treatment.

In the Test Dose phase of Study 401, there were 18 SAEs which occurred in 14 patients. Of those that occurred within 48 hours after treatment, there were 2 SAEs that occurred in 2

patients that are outlined below, and they did lead to discontinuation from the study.

- (b) (6), 63-year-old male patient, who developed an SAE of sedation 10 minutes after the second 5 mg dose of MDZ NS. Concomitant medications included lamotrigine, and lacosamide for seizures, rivastigmine transdermal patch, and memantine hydrochloride for memory as well as folic acid, vitamin B12 and allergy shots. After the second dose, he immediately became confused, and stopped following commands. About 9 minutes after the second dose he became “unresponsive” to nail bed pressure or sternal rub, and experienced salivary hypersecretion with cough. His BP was 94/68, respiratory rate was 14 bpm, and oxygen saturation maintained at 97%. The acute care team responded, administered oxygen and flumazenil 0.2 mg by intravenous push and a normal saline fluid bolus. Within minutes the patient responded, and vitals remained stable. He was transferred to ER for observation, where he was alert and was discharged home. His confusion was completely resolved less than 4 hours after the dose.

Reviewer’s note: This event is concerning for a patient to become unresponsive and require a dose of flumazenil, a benzodiazepine antagonist, in response to treatment. However, it was reassuring that despite the unresponsiveness and confusion, the patient maintained his airway and his oxygen saturations the entire time. He also had risk factors for confusion and sedation given his diagnosis of “memory problems” and concurrent treatment with memantine and rivastigmine. He may have been someone who should not have received the 2nd dose of MDZ.

- (b) (6), 48-year-old male patient, experienced an SAE of somnolence. He received the first dose of 5 mg MDZ NS (test dose) at 10:10 am. He did not receive a second dose. About 7.5 minutes later, he was somnolent and could not speak or open his eyes. After 10 minutes, he was unarousable. After 1.5 hours, he was arousable and could be awakened with physical stimulation, and he awoke spontaneously 3.5 hours after dosing. He did also experience concurrent oxygen desaturation with recording of 89% for an undisclosed duration. Concomitant medications included levetiracetam and lacosamide. He was discontinued from the study. His BP was elevated (150-160/90-100) for the duration of treatment and observation, and his pulse and respiration rate remained stable.

Reviewer’s comment: This patient experienced excessive somnolence after a single 5 mg dose, he had mild oxygen desaturation to 89% briefly during this time. He did not require any medical intervention and spontaneously awoke after a few hours. Had he received the treatment during a seizure cluster, he may have been considered post-ictal and recovered without significant medical concerns.

I also reviewed the remaining 12 patients in the Test Dose Phase who had SAEs which occurred more than 48 hours after study drug administration. Among those, 3 patients had 4 SAEs that

resulted in discontinuation from the study.

- (b) (6), 62-year-old female patient developed Rocky Mountain Spotted Fever 3 months after the Test Dose was given, but prior to randomization/Visit 3, which resulted in study discontinuation (Visit 3 postponed for DSMB initial review)
- (b) (6), 36-year-old female patient diagnosed with status epilepticus and conversion disorder 4 months after Test Dose, but prior to randomization/Visit 3, resulting in study discontinuation (Visit 3 postponed for DSMB initial review)
- (b) (6), 32-year-old female patient had an SAE of “seizure cluster” that was mild, but resulted in hospitalization, 9 days after the Test Dose was administered.

There was only one SAE that was considered respiratory-related, which was a mild episode of hypoxia 6 weeks after study drug administration in a patient that did not discontinue from the study. It was felt to be exacerbation of chronic respiratory failure (Patient (b) (6)).

In the open-label extension Study 402, there were 45 SAEs in 18 patients. The only ones to occur in > 1 patient were those related to seizures (seizure cluster, convulsion, epilepsy, and status epilepticus). For those clinically relevant SAEs that occurred within 48 hours after the dose of study drug, there were 8 patients who had 13 SAEs. Among those, the SAEs were seizure cluster (3), status epilepticus (2), convulsion (3), epilepsy (1), BP increased (1), and seizure cluster, pyrexia, and nausea concomitantly in one patient. Only two patients with SAEs led to discontinuation, and did not occur within 48 hours of drug administration. These are detailed below:

- (b) (6) - 18-year-old female patient discontinued due to development of necrotizing, hemorrhagic pancreatitis, cholelithiasis, renal infarct, anemia, and portal vein thrombosis, which did not occur at the time of study drug administration
- (b) (6) - 19-year-old female patient discontinued for an SAE of “multiple seizures” that required hospitalization. She had previously treated 4 seizure clusters in the month preceding this SAE.

There were no recorded SAEs in Study 301 or Study 408.

Reviewer's Comment: In an acute, single-event, treatment trial such as the Comparative Phase of Study 401, it is difficult to have discontinuation due to an AE, as the study is only designed to be a single acute treatment, so unlikely that any AE occurring after treatment would result in discontinuation. Therefore, it is less significant that the SAEs in the Comparative Phase did not lead to discontinuation. However, in the case of both above-described SAEs from the Comparative Phase, they were consistent with the patients' baseline seizure clusters and were unlikely to be related to the drug, although they may have been due to lack of efficacy of the study drug (one patient initially received placebo). The SAEs that occurred in the Test Dose Phase that resulted in discontinuation and exclusion from randomization that are detailed above are more significant, despite the lack of a placebo comparator arm in that phase of the study

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no TEAEs in the Comparative Phase that led to discontinuation. As noted above, given the study design as an acute, single-event treatment with rapid follow-up visit, it is unlikely that a TEAE in the acute treatment phase of the study would lead to discontinuation.

However, in the Test Dose Phase, there were 16 patients with a total of 30 TEAEs who discontinued secondary to an adverse event (Table 21). Of these, 14 patients discontinued prior to randomization, and 2 discontinued after randomization but prior to treatment in the Comparative Phase. Many of these were protocol-driven due to the discontinuation criteria after receipt of Test Dose. Five of these patients, italicized in Table 21, had SAEs and are detailed above in Section 8.4.2. Those with respiratory AEs are in bold, and will be described in detailed below in Section 8.4.4. The TEAEs leading to discontinuation that occurred in more than 1 patient were sedation (4), O2 saturation decreased (3), and somnolence (3), and throat irritation (2), all of which occurred within 48 hours of study drug administration.

Table 21 Discontinuations due to Adverse Events in Test Dose Phase

Subject ID	TEAEs leading to D/C	48 hours? Y/N	SAE? Y/N	Resp AE? Y/N
(b) (6)	<i>Rocky mountain spotted fever</i>	N	Y	N
	<i>Status Epilepticus</i>	N	Y	N
	<i>Conversion Disorder</i>	N	Y	N
	Somnolence	Y	N	N
	Dyspnea	Y	N	Y
	Respiratory rate decreased	Y	N	Y
	O2 saturation decreased	Y	N	Y
	Sedation	Y	N	N
	Dizziness	Y	N	N
	Hypotension	Y	N	N
	Respiratory rate decreased	Y	N	Y
	Sedation	Y	N	N
	Throat irritation	Y	N	N
	Product taste abnormal	Y	N	N
	Nasal discomfort	Y	N	N
	<i>Sedation</i>	Y	Y	N
	Sedation	Y	N	N
	<i>Somnolence</i>	Y	Y	N
	O2 saturation decreased	Y	N	Y
	Diplopia	Y	N	N
	Throat Irritation	Y	N	N
	Anxiety	Y	N	N
	Flushing	Y	N	N
	Gait Disturbance	Y	N	N
	Hypersomnia	Y	N	N
	O2 saturation decreased	Y	N	Y
	<i>Seizure cluster</i>	N	Y	N
	Sodium low	N	N	N
	Seizure cluster	N	N	N
	Somnolence	Y	N	N

Source: Reviewer's analysis of Study 401 ADAE dataset

^a Described above in Section 8.4.2, SAEs leading to discontinuation in Test Dose Phase

^b Described below in Section 8.4.4, Respiratory AEs leading to discontinuation in Test Dose Phase

*Patient was randomized but then discontinued prior to treatment in Comparative Phase

Among these 16 patients that discontinued after receiving the test dose, 10 were female and 6 were male. One of the patients was 18 years of age, 14 patients were 18 to < 65 years of age, and 1 patient was ≥ 65 years of age. There were no clear identifying factors in terms of enzyme-inducing status, BMI, concomitant medication use, or medical history that contributed to which patients had a higher risk of discontinuation.

In the open-label extension study (Study 402), there were four patients who discontinued due to TEAEs. Two of them were SAEs and are outlined above in Section 8.4.2. The other two are detailed below:

- (b) (6) - 20-year-old female patient discontinued for a TEAE of severe nasal discomfort,

but had previously treated 8 seizure clusters in the preceding 18 months on the long-term extension study.

- (b) (6) – 41-year-old male patient discontinued for an episode of moderate somnolence after his first treated seizure cluster in the long-term study.

In study 408, there were no patients leading to discontinuation. However, one patient (b) (6) had a TEAE of mild O2 sat decreased to 87% for 2 minutes, associated with moderate somnolence, and only received the test dose. Study 301 was a single-dose treatment and no TEAEs led to discontinuation.

Reviewer's comment: Among the TEAEs leading to discontinuation in the open-label extension study, there are no new or concerning safety signals. There was one patient who discontinued due to nasal discomfort and one due to somnolence, both of which were likely related but not unexpected. The two patients who discontinued due to SAEs were unlikely related to the study drug. Of note, the patient with nasal discomfort discontinued after treatment of 8 seizure clusters over an 18-month period of time, which did not exceed maximum recommended frequency of treatment in the study.

8.4.4. Significant Adverse Events

Significant adverse events discussed in this section include TEAEs that were coded as severe in intensity, as well as TEAEs that were noted as AEs of special interest.

In the Comparative Phase of Study 401, there were 6 severe TEAEs in 4 patients, all of which started within 48 hours of study drug administration. None of them were also classified as SAEs. They were headache, nausea, vomiting, nasal discomfort (2) and somnolence. In the Test Dose phase, there were 27 severe TEAEs in 20 patients. Of these severe AEs, four AEs led to discontinuation and are discussed in Section 8.4.2 and Section 8.4.3 above. Of those that occurred within 48 hours of test dose being given, 11 patients had 13 severe TEAEs, which included eye irritation or pain, sedation, cough, oropharyngeal pain, nasal discomfort (2), and somnolence (7).

TEAEs that were in the respiratory class were of special interest to the development program because of prior knowledge about benzodiazepines and potential for respiratory depression. There were no TEAEs in the respiratory SOC that occurred in the Comparative Phase.

However, in the Test Dose phase, there were 12 TEAEs in 10 patients in the respiratory class. Among these, 6 patients had TEAEs occurred within 48 hours of the study drug administration and led to discontinuation from the study. In a few cases, the discontinuation was protocol-driven, or not related to the respiratory AE but other significant AEs. Table 22 Patients with Respiratory TEAEs in Study 401, Test Dose Phase provides further detail about these 6 patients who discontinued due to respiratory TEAEs.

Table 22 Patients with Respiratory TEAEs in Study 401, Test Dose Phase

Subject ID	Respiratory TEAE	Associated TEAEs	Total Test Dose	Prior Benzos (Y/N)	Potential risk factors/ Other notes
(b) (6)	Dyspnea	Nasal discomfort, cough, throat irritation and pain, somnolence, dizziness, malaise	5 mg	Y	On phenobarbital, O2 sat 94%
	Resp rate decreased O2 sat decreased	Sedation, dizziness, hypotension, dizziness	5 mg	Y	RR 14 → 10 bpm, O2 sat 99% except for during a 1 min seizure occurred after 10 min
	Resp rate decreased	Sedation	5 mg	Y	h/o asthma/dyspnea RR 7 bpm
	O2 sat decreased	Somnolence	5 mg	?	O2 sat 89% while unarousable
	O2 sat decreased	Diplopia, throat irritation, anxiety, flushing, gait disturbance	5 mg	?	O2 sat 87% x 1 minute (mild), d/c due to other sx
	O2 sat decreased	none	10 mg	Y	h/o sleep apnea, somnolence O2 sat 81-84%

Source: Clinical Reviewer Analysis of Study 401 ADAE, ADSL datasets

*Patient reviewed in Section 8.4.2 above as SAE leading to discontinuation

Reviewer's note: Of these 6 patients who did not continue into the Comparative Phase of treatment, the respiratory-related TEAEs were mild in the majority of patients, including desaturations just below 90% that were self-limited or rapidly resolving in a few patients. The patient who had a reported decreased respiratory rate was because of an overall change in respirations (14 bpm to 10 bpm), but the respiratory rate itself was not dangerously low. That patient also did have decreased O2 saturation, but that was only during a 1 minute seizure that the patient suffered shortly after drug administration. A brief O2 desaturation is not unexpected during a seizure.

The patient with the most significant reduction in O2 saturation may have had a lower O2 saturation at baseline, and did not have any other associated TEAEs at the time of his marked O2 saturation decrease. He had a history of sleep apnea, which may be an indicator of someone who should be given a test dose prior to outpatient dosing.

Amongst the 10 patients with respiratory TEAEs, I was unable to identify any clear risk factors in

terms of age, demographics, BMI, concomitant medication use, or medical history. Specifically, among the 6 patients that had respiratory AEs within 48 hours of dosing, which led to study discontinuation, 1 patient was 65 years of age, 1 patient was 17 years of age, and 4 patients were 18-64 years of age. Of the 6 patients, four of them did have significant medical history, including 2 patients with prior lobectomy, 2 patients each with asthma, 2 patients each with drug hypersensitivity, increased cholesterol, osteopenia, seasonal allergy, and 1 patient with a history of sleep apnea.

Reviewer's comment: There were no clear risk factors identified for which patients may not tolerate the treatment. However, the small numbers of patients that had respiratory events, and the lack of severity of such events, is reassuring. Of note, it was interesting to see that at least 4 of the 6 patients who had a respiratory TEAE used intermittent benzodiazepines for rescue treatment already, so they were not "benzo-naïve". It is possible that administration of the drug in a more controlled-environment in the absence of seizure made adverse events (such as O2 saturation decreased or somnolence) more apparent than they would have been if they occurred in the post-ictal phase in an outpatient setting without protocol-specified monitoring. The only patient that required a medical intervention was for somnolence, and that patient is discussed above in section 8.4.2.

In the open-label extension Study 402, only 2 patients were flagged as having respiratory-related TEAEs. One patient experienced a mild TEAE of oxygen saturation low (b) (6) which occurred at the time of treatment, however, it did not lead to discontinuation, and this patient treated 73 clusters over a period of 50 months. Another patient (b) (6) was diagnosed with sleep apnea, not related to a study drug treatment, which did not lead to discontinuation and the patient was enrolled for 20 months and treated 15 seizure clusters with no other related TEAEs.

In Study 301 there were 2 severe TEAEs, one of shoulder pain (MDZ NS arm) and one of headache (in placebo arm). There were no respiratory-related TEAEs.

In Study 408 there were no severe TEAEs. There was one mild O2 saturation decreased recorded in the Test Dose who did not continue to receive the outpatient treatment.

I also looked at the patients in Study 401 who had TEAEs that were flagged as "Taste and Smell Disorders" or "Route of Administration-Related". All of the TEAEs flagged for Taste and Smell disorders were coded as "product taste abnormal" and occurred in 20 patients, at the time of dosing. There were 83 patients who had 184 TEAEs of nasal discomfort or throat irritation, with 6 being severe, and 3 leading to discontinuation. None resulted in SAEs. There were no TEAEs indicative of olfactory toxicity (See Section 8.5.3).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In the Study 401 Test Dose phase, the most common TEAEs that occurred within 48 hours of drug administration in the 292 patients were nasal discomfort (18%), somnolence (10%), product taste abnormal (6%), lacrimation increased (7%), throat irritation (5%), and rhinorrhea (5%). Other TEAEs that occurred in at least 2% of the population were sedation, dizziness, oropharyngeal pain, sneezing, cough, and eye irritation or pain. See Table 23.

Table 23 TEAEs Occurring in $\geq 2\%$ of the Test-Dose Population in Study 401

Adverse Event	N ^a	% Total N = 292
Nervous System		
Somnolence	29	10%
Sedation	10	3%
Dizziness	8	3%
Application Site AEs		
Nasal discomfort	53	18%
Product taste abnormal	17	6%
Throat irritation	15	5%
Rhinorrhoea	14	5%
Oropharyngeal pain	11	4%
Sneezing	5	2%
Cough	6	2%
Eye Disorders		
Lacrimation increased	20	7%
Eye irritation and pain	5	2%

^a Includes TEAEs that occurred within 48 hours of drug administration

Source: Clinical Reviewer's Analysis of Study 401 ADAE dataset

In the double-blind, controlled, Comparative Phase of Study 401, the most common TEAEs noted that occurred within 48 hours of study drug administration are outlined below in Table 24.

Table 24 Table of Comparative Phase AEs^a that are ≥ 2% in Nayzilam Treatment group and Greater than Placebo

Adverse Event and System	Placebo	Nayzilam			
		Placebo + 5 mg Nayzilam	Nayzilam 5 mg	Nayzilam 5 + 5 mg	Any Nayzilam
	N = 26 (%)	N = 41 (%)	N = 91 (%)	N = 43 (%)	N = 175 (%)
Nervous System					
Somnolence	4	10	10	9	10
Headache	0	0	7	2	4
Dysarthria	0	2	2	2	2
Application Site AEs					
Nasal Discomfort	8	7	5	16	9
Throat Irritation	0	2	2	7	3
Rhinorrhoea	0	0	3	5	3
Product Taste Abnormal	0	0	4	0	2
Eye Disorders					
Lacrimation Increased	0	2	1	2	2

^a Adverse Events that Occurred within 2 days of Nayzilam administration are included

Source: Clinical Reviewer's Analysis of Study 401 ADAE dataset

Reviewer's comment: Of note, because all patients who did not respond to the initial dose were given the opportunity for an open-label 5 mg dose MDZ NS between 10 minutes and < 6 hours after dosing, the pool of placebo patients is decreased. The open-label nature of the second dose may also confound the results; however, overall the AE profile in the open-label Test Dose Phase is very similar to the AEs seen in the Comparative Phase, and is consistent with both known AE profile of midazolam from the approved product, as well as expected AEs given the intranasal route of administration.

In the long-term extension Study 402, the most frequent TEAEs in the 161 patients treated were nasal discomfort (15%), headache (11%), seizure (10%), somnolence (9%), and lethargy/malaise/fatigue (8%). Other TEAEs that occurred in more than 2% of the population were nasopharyngitis, upper respiratory tract infection, dizziness, nausea, rhinorrhea, sneezing, urinary tract infection, back pain, hypertension, and throat irritation.

In Study 301 the most frequent TEAEs were nasal discomfort (same as placebo), nausea, and somnolence.

Reviewer's comment: The common TEAEs in the open-label extension trial (Study 402) did not reveal any new TEAEs that were more severe or significant, and were overall consistent with the findings in Study 401 and the known adverse event profile of MDZ.

8.4.6. Laboratory Findings

The changes from baseline in hematology and serum chemistry laboratory tests were analyzed

and summarized by the applicant and verified by this reviewer. For all hematology parameters, there were no notable differences in baseline levels between treatment groups in Study 401. The mean changes from baseline were small and there were no differences between treatment groups. Serum chemistry analyses also showed no clinically meaningful changes observed with respect to median changes from baseline for any serum chemistry values in either MDZ NS or placebo treated patients. A noted increase in mean serum creatinine level following single MDZ NS treatment was attributed to a lab error, with an outlier value reported of 8575 umol/L, rather than 0.875 umol/L.

8.4.7. Vital Signs

Vital signs were measured at each visit and corresponding changes from baseline were analyzed. No notable differences or trends were noted between the treatment groups.

8.4.8. Electrocardiograms (ECGs)

There were some abnormal ECG findings found at Visit 1, Visit 2 pre-dose, and Visit 2 post-dose (15 minutes). However, only 1 abnormal ECG was considered clinically significant, and it was identified at Visit 1 (screening). There were no clinically significant ECG results noted at Visit 2 pre- or post-dose. Of those patients who did have abnormal ECGs (not clinically significant), there were relatively equal proportions between those randomized to MDZ NS and those randomized to placebo in the Comparative Phase.

8.4.9. QT

Not studied.

8.4.10. Immunogenicity

Not applicable. Midazolam is a small molecule.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Acute Central Respiratory Depression

See Section Significant Adverse Events 8.4.4 above.

8.5.2. Depression and Suicidality

The C-SSRS is a validated assessment of suicide risk and was utilized in all the MDZ NS studies. Across all studies, similar proportions of patients from MDZ NS and placebo groups had

baseline and post-baseline assessments for suicidal ideation. One patient from the MDZ NS treatment group had treatment-emergent suicidal ideation at post-baseline with increase in maximum score of 2. There were no reported TEAEs of suicidal ideation or suicidal behavior.

Reviewer's comment: There was no significant concern for suicidality for this chronic, intermittent therapy, which will be used for acute exacerbations of seizures. As depression and suicidal ideation are common in epilepsy patients, the warning may still be included in the label despite lack of significant concern with this particular treatment and indication for use.

8.5.3. Nasal and Olfactory Toxicity

Nasal and Olfactory Toxicity were among the AEs of special interest for this application. Among all studies, there were no reported TEAEs indicative of olfactory toxicity or nasal toxicity. Nasal examinations revealed no nasal abnormalities recorded as clinically significant at any visit.

We had requested the addition of the B-SIT to studies 401, 402, and 408 for evaluation of olfactory toxicity. However, at the time of the request, studies 401 and 402 were already well into enrollment, limiting the number of patients for whom the applicant was able to obtain baseline B-SIT scores for. Also, the early termination of Study 408 for business reasons also limited the number of patients who had B-SIT assessments. Furthermore, the B-SIT was limited to the United States because of concern over lack of test validation in other languages/cultures. It was also limited by the inability to implement the test in patients who were not cognitively capable of participating.

However, the data that was obtained from the 3 studies did not indicate any likelihood of meaningful impact on olfaction. In Studies 401, 402, and 408, there were 23 patients who underwent treatment for at least 1 year and had both a baseline and post-Test-Dose B-SIT assessment for olfactory toxicity. Three patients had treated at least 3 seizure cluster episodes and had at least 1 year between the baseline and last B-SIT assessment.

In Study 401, there were comparable mean and median B-SIT scores at baseline for those randomized to MDZ NS (n = 12) and those randomized to placebo (n = 3). After administration of the test dose, the mean and median B-Sit scores were slightly higher at Visit 3 for the patients randomized to MDZ NS compared to placebo. And of the 13 patients who then had B-SIT data after administration of the double-blind dose, the mean and median change from baseline was negative in the patients assigned to placebo (mean = -0.3), as compared to positive in patients assigned to MDZ NS (mean = 0.7). The numbers are too small and limit ability to draw any conclusions.

The published literature analysis of nasal and olfactory toxicity is intended to support the application because of the limited data noted above. The applicant performed an extensive literature search on the local effects of IN administration of midazolam.

The applicant provided references for 50 clinical trials and observational studies (21 double-blinded, randomized and controlled studies) of over 1500 children and adults with safety data reported associated with use of intranasal midazolam. Many of these studies relied on intranasal administration of the parenteral formulation of MDZ that is commercially available. The midazolam was administered intranasally via syringe or with an atomizer device. None of the studies reported any SAEs associated with IN administration, and no olfactory adverse events were reported.

The documented local adverse events reported in the literature including nasal stinging/burning, local irritation, lacrimation, sneezing, coughing, rhinorrhea, and bitter taste, which were common and transient, and usually mild to moderate in severity, and not lasting more than 30 minutes. Among the published literature, there were 3 pharmacokinetic/pharmacodynamic studies of a novel, aqueous, MDZ formulation that was formulated specifically for intranasal use, that objectively evaluated nasal mucosal toxicity in a total of 45 healthy subjects, who received a total of 78 intranasal exposures.^{8,9,10} The endoscopic examination of the nasal mucosa by an ENT in these studies revealed no significant abnormalities. There were mild, transient, and localized mucosal abnormalities visualized in 2 subjects which both spontaneously resolved. Two of the studies also objectively investigated olfactory toxicity^{7,8}, with 33 subjects who received a total of 66 exposures, with no reported alteration in smell or loss of smell.

Reviewer's comment: The described local adverse events in the literature are similar to the reported "route of administration TEAEs" that were commonly seen in the clinical studies. As noted by the applicant, the literature primarily describes intranasal administration of the parenteral formulation, and thus, some of the local adverse events reported may have resulted from the low PH, excipients, larger volume of solution, or force of spray into the nose that are not expected to be a concern with the proposed MDZ NS formulation. The 3 studies of a more concentrated, aqueous intranasal formulation that objectively looked at nasal and olfactory toxicity in healthy subjects was reassuring for lack of any significant associated toxicity.

⁸ Wermeling DP, Record Ka, Kelly TH, et al. Pharmacokinetics and pharmacodynamics of a New Intranasal Midazolam Formulation in Healthy Volunteers. *Anesthesia and Analgesia* 2006; 103(2): 344-349.

⁹ Wermeling DP, Record KA, Archer SM, Rudy AC. A Pharmacokinetic and Pharmacodynamic Study, in Healthy Volunteers, of a Rapidly Absorbed Intranasal Midazolam Formulation. *Epilepsy Research* 2009; 83:124-132.

¹⁰ Schrier L, Zuiker R, Merkus FWHM, et al. Pharmacokinetics and pharmacodynamics of a new highly concentrated intranasal midazolam formulation for conscious sedation. *Br J Clin Pharm* 2017; 83:721-731.

Furthermore, it was noted that in 2 studies of 21 adult patients¹¹ and 22 pediatric patients¹², both patients (adult) and caregivers (both adult and pediatric studies) greatly preferred intranasal MDZ over rectal diazepam.

Reviewer's comment: The applicant did provide an analysis of the risk of nasal and olfactory toxicity for Study 401 and 402. However, the late implementation of the B-SIT for olfactory toxicity, as well as limitation to the US population, and difficulty with compliance, make it difficult to interpret the small number of patients. However, the lack of significant TEAEs of olfactory or nasal mucosal toxicity, including lack of abnormal findings on nasal exams throughout the study is reassuring. The literature is also reassuring. There are over 1,500 patients treated in the presented literature with intranasal MDZ, and the formulation used in those studies is likely more abrasive and potentially toxic given the low pH of the parenteral formulation. There was no report of any significant nasal mucosal or olfactory toxicity in the literature, even in the studies with dedicated safety analyses of such toxicity. Despite concerns for publication bias, and the lack of patient-level safety data from these trials, it seems that there is low risk for nasal toxicity given the intended frequency of use of the MDZ NS product.

8.5.4. Dosage/CYP3A4 inhibitors

As noted in the Clinical Pharmacology review, there is significant concern for increased exposures when MDZ NS is given concomitantly with moderate or strong CYP3A4 inhibitors. It is believed that use with concomitant moderate CYP3A4 inhibitors would result in much higher exposures, and the exposures with concomitant CYP3A4 strong inhibitors would result in approximately 5-fold higher exposures. As such, given that patients may use Nayzilam they have at home without first discussing new medications with their providers, avoidance of concomitant moderate or strong CYP3A4 inhibitors will be recommended in labeling.

This reviewer does note that in Study P261-201, a Phase 1 Tolerability study in Subjects with Epilepsy, the safety and tolerability of doses up to 20 mg in single and two-dose regimens was evaluated. Study 201 was a randomized, double-blind, placebo-controlled, dose-escalation study. The patients in the study were assigned sequentially to 1 of 4 cohorts, and were randomized to receive MDZ NS to placebo in a 4:1 ratio. Cohorts were composed of 15 patients and assigned a single dose level of 10, 15, 17.5, or 20 mg of MDZ NS or matching placebo. The

¹¹ De Haan, GJ, van der Geest P, Doelman G, Bertram E, Edelbroek P. A Comparison of Midazolam Nasal Spray and Diazepam Rectal Solution for the Residential Treatment of Seizure Exacerbations. *Epilepsia* 2010; 51(3):478-482.

¹² Harbord MG, Kyrkou NE, Kyrkou MR et al. Use of Intranasal Midazolam to Treat Acute Seizures in Paediatric Community Settings. *J Paediatr Child Health* 2004; 40:556-558.

doses were administered as a single dose at Visit 2, and then as a divided dose (5 + 5, 7.5 + 7.5, 10 + 7.5, 10 + 10) given 10 minutes apart at Visit 3.

There were a total of 60 patients, 48 patients assigned to MDZ NS and 12 patients randomized to placebo. There were no deaths, no SAEs, no TEAEs leading to discontinuation of study medication, and it was concluded that single and repeat doses of 20 mg MDZ NS were well tolerated. The occurrence of TEAEs was not clearly related to dose, and more importantly, no TEAEs of respiratory or cardio-respiratory efforts were reported, and no O₂ saturations < 90% were observed, even in those who received 20 mg MDZ NS. Assessments using the OAA/S scale revealed evidence of sedation in patients receiving MDZ NS relative to placebo that occurred rapidly and returned to baseline by 4 hours post-dose.

Reviewer's comment: Although a Phase 1 study, this study does demonstrate tolerability up to a dose of 20 mg of MDZ NS given as a single dose or as a divided dose (10 + 10 mg) with no TEAEs of respiratory effects or O₂ saturation decreased. Drug-drug interactions with moderate CYP3A4 inhibitors are expected to increase the exposure by 2-3x, and this information will be labeled as a Warning. However, because some patients may take Nayzilam without discussing with their doctor first, especially if they have just been prescribed a new medication, these data are reassuring that higher doses may be tolerated by many patients.

8.5.5. Test Dose Requirement

In Study 401, all patients received a test dose prior to enrollment in the outpatient, caregiver-administered Comparative Phase. Therefore, discussions were raised during development whether the drug would only be approved with a requirement for a test dose for safe use in the community. For this analysis, I considered the discontinuations in the Test Dose Phase, as well as respiratory adverse events in any phase of treatment, and the studied and proposed patient population.

Reviewer's comment: At this time, I would not recommend a test dose be given prior to use in the outpatient setting for several reasons. The overall AE profile in the MDZ NS studies was good, and the drug was very well tolerated. There were no SAEs related to acute central respiratory depression. Most of the TEAEs were mild or moderate, and those that were severe tended to be most related to administration, and were transient. Other severe TEAEs appeared related to underlying seizure disorder, or were removed from and unrelated to the study drug treatment.

Of the two patients who discontinued treatment due to SAEs after the Test Dose Phase, one of them required a dose of flumazenil for excessive sedation and confusion. However, this patient had co-morbid cognitive and memory concerns, and was on rivastigmine and memantine, which may have contributed to the development of confusion and sedation. He is not a typical patient who will be prescribed such a treatment, and care should be used before

giving to patients with certain pre-existing conditions. The second patient with an SAE leading to discontinuation had self-resolving somnolence, which was severe, and resulted in mild O2 saturation decrease, but may have been an unrecognized adverse event had he been having a seizure cluster or had he been post-ictal.

The risk for certain adverse events, such as somnolence, is much higher when giving a test dose to patients in the absence of a seizure. Other AEs such as nasal discomfort and throat irritation may also be more irritating to patients who are administered the drug in the absence of a seizure. Requiring a test dose in this setting to all patients prior to use may greatly increase the chances that the patient may experience a negative adverse event and then choose not to take it during a seizure cluster when it is clinically indicated.

Finally, I believe that clinically it would be very challenging to require a test dose prior to prescribing because of time and resource limitations in the outpatient clinic, as well as insurance reimbursement for drug product that would need to be stored in clinic. If the drug was not already available to be provided to the patient for the test dose, patients would need to fill their prescription, and then return for a prolonged visit with a caregiver to drive them home that would require administration of the test dose and 1-2 hours of monitoring. This would require significant resources for the patient and the prescribing physicians and would likely not be practicable. Furthermore, several formulations of benzodiazepines are currently prescribed as rescue medications (both on and off-label) for intermittent seizures, anxiety, and panic attacks, all of which are used in the outpatient setting, and none of which require a test dose to be given. Although this is a new route of administration, the risk of adverse events is not higher than with any other approved product.

However, given the results of the human factors studies, and the unique features of the device which actuates easily, patients and caregivers do need to be taught carefully how to administer the medication, and should be required to practice either actuating a training device, or administering a "sham dose" of saline, to be sure that they will be able to accurately use the device when it is needed. There may also be certain high risk patients with other pre-existent medical condition is or concomitant medications that may benefit from a test dose at the discretion of the provider.

8.6. Safety Analyses by Demographic Subgroups

Age

No clinically relevant differences in the frequency of TEAEs were noted in age groups < 18 years, 18 to < 65 years, and ≥ 65 years of age. The small numbers of patients in each age group limit the ability to sufficiently compare safety by age group.

Sex

The overall frequency of adverse events was similar among male and female patients. There were some sex differences in the frequency of some TEAEs, of unclear clinical significance. Females reported higher incidence ($\geq 5\%$ difference) of somnolence, and nasal discomfort during the Comparative Phase of Study 401, and a higher incidence of throat irritation during the Test Dose phase. There was a higher incidence of product taste abnormal reported by male patients.

Race

There were 17 non-white patients who received MDZ NS during Study 401 Test Dose Phase, and the only TEAEs reported for more than 1 non-white patient were nasal discomfort (4), oropharyngeal pain (2) and sedation (3). There were no TEAEs reported for more than 1 non-white patient in the Comparative phase. In the combined pool from Studies 401 and 402, the frequency of TEAEs was similar in the Non-white and white patient populations, and there were less than 10% of patients who were non-white, limiting any comparisons across race.

BMI/Weight

A safety analysis based on weight and BMI in Study 401 was completed, given that MDZ NS was given as a fixed dose throughout product development. There were no TEAEs with $\geq 5\%$ difference by weight during the Test Dose phase, while the incidence of nasal discomfort was higher in the "less than median weight" group (< 71.6 kg) than in the "greater than or equal to median weight" group (≥ 71.6 kg), during the Comparative Phase.

In the combined pool from Studies 401 and 402, there were differences by weight seen with higher incidence of somnolence and convulsion in the < 71.76 kg weight group, and higher incidence of hypertension in the ≥ 71.76 kg. These TEAEs are not clinically significant. The lower incidence of somnolence in the higher weight group may be due to lower overall systemic exposures.

For BMI analysis, patients were grouped as "underweight and normal" ($\text{BMI} < 25 \text{ kg/m}^2$), "overweight" ($\text{BMI} \geq 25$ and $< 30 \text{ kg/m}^2$), and "obese" ($\text{BMI} > 30 \text{ kg/m}^2$). There were no TEAEs with large difference between BMI groups during the Test Dose or Comparative Dose Phase.

Other

TEAEs were also analyzed by geographic location, enzyme-induced status, and number of concomitant seizure medications. Patients in North America and similar (Australia, New Zealand) reported more TEAEs including somnolence than patients in other regions. Based on exposure to enzyme-inducing AEDs there was a $\geq 5\%$ difference between patients considered "enzyme-induced" to "non-enzyme-induced" for lacrimation increased during the Test Dose phase and for somnolence during Comparative dose phase.

The incidence of nasal discomfort was lower and fatigue/lethargy higher in patients exposed only to non-enzyme inducing AEDs vs those exposed to enzyme inducing AEDs. Potentially this

finding could be because of differences in systemic exposures based on Population PK analysis. It was not a clinically relevant difference in the incidence of somnolence that was higher in those patients exposed to non-induced AEDs vs patients exposed to inducing AEDs.

Abuse-Related TEAEs

See full review by CSS. Benzodiazepines have known drug abuse potential, and midazolam is listed as a Schedule IV controlled substance. Adverse events related to potential abuse were reported as an AE of significant interest.

The incidence of potentially abuse-related TEAEs was higher with MDZ NS compared to placebo, and the majority of events were mild or moderate in severity. The CNS depressant TEAEs of somnolence and fatigue, as well as dizziness were the most commonly reported, as expected with the known adverse event profile of MDZ. Less commonly observed were other abuse-related TEAEs such as sedation, euphoric mood, feeling abnormal, as well as any perceptual disturbances, stimulation/anxiety symptoms, or mental and cognitive impairment.

8.7. Specific Safety Studies/Clinical Trials

No such studies performed.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Data is reliant on the listed drug.

8.8.2. Human Reproduction and Pregnancy

Data is reliant on the listed drug.

8.8.3. Pediatrics and Assessment of Effects on Growth

Safety data is reliant on the listed drug. PREA is not triggered because of the orphan drug status, and thus post-marketing requirements are not planned. (b) (4)

In Study 401, there were a total of 18 patients < 18 years of age who received MDZ NS during the Test Dose Phase, and 8 patients who received MDZ NS during the comparative phase. There was one patient who was < 18 years of age in Study 301. The TEAEs reported for more than 1 pediatric subject were nasal discomfort, oropharyngeal pain, and dizziness, which were each reported for two patients in the Test Dose Phase.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data is reliant on the listed drug. See full CSS review.

As listed in the Diastat label, "Chronic daily use of benzodiazepines may increase the frequency and/or severity of tonic-clonic seizures, requiring an increase in the dosage of standard anticonvulsant medication. In such cases, abrupt withdrawal of chronic benzodiazepines may also be associated with a temporary increase in the frequency and/or severity of seizures."

Reviewer's comment: Treatment in the open-label extension study were treated no more than every 3 days. Chronic daily treatment with MDZ is not recommended. The above statement from the Diastat label on chronic use and concern for tolerance and withdrawal symptoms represents a class effect and should be included here as well. There should be no implication that MDZ NS is any safer in that regard than use of rectal diazepam. It is recommended that MDZ NS not be used to treat more than 5 seizure episodes in a month.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There is no postmarket experience of this drug product. There are well-established safety issues present in the reference listed drug label from prior experience with midazolam in other indications/uses.

8.9.2. Expectations on Safety in the Postmarket Setting

Postmarket safety is expected to be in alignment with the established use of benzodiazepines in treatment of acute seizures.

8.9.3. Additional Safety Issues From Other Disciplines

None.

8.10. Integrated Assessment of Safety

The safety profile of Nayzilam is consistent with the known AE profile of midazolam, as well as other benzodiazepines, such as diazepam and lorazepam. There is no safety signal identified in the reviewed studies or published literature for any new or unique safety concerns. Although there is a risk with benzodiazepine treatment for acute respiratory depression, there were no deaths and no SAEs of acute respiratory depression in the development program. The literature and the reviewed studies do not demonstrate any evidence for nasal mucosal or olfactory toxicity.

The unresolved questions are for appropriate treatment frequency and risk for use with concomitant medications because of drug-drug interactions. In the long-term extension study, patients were allowed to treat subsequent seizure clusters no more than every 3 days. A few patients did use it several times a week or month with no increase in TEAEs. As noted above in Section 8.8.4, there is also potential concern for dependence if used chronically. Therefore, I recommend that labeling state that treatment should not be used more frequently than every 3 days, and no more than 5 episodes in a month.

In terms of concomitant medications, strong CYP3A4 inhibitors are expected to increase the exposures approximately 5-fold and should be avoided. Moderate CYP3A4 inhibitors are more commonly used, and will also have a significant (2-3 x) increase in exposure. However, although these will be cautioned in the label, it is possible that patients will utilize MDZ NS as rescue medication if they have it at home, without telling their physician that they are taking another new medication which may be a moderate CYP3A4 inhibitor. The PK Phase 1 dose-range study demonstrated safety and tolerability of up to 20 mg MDZ NS with no SAEs and no respiratory depression, which is reassuring in the event of unintentional combination with a moderate CYP3A4 inhibitor.

Although a test dose was required prior to outpatient treatment in the community, I do not feel that it will be necessary for approval of the drug, as discussed in Section 8.5.5. Although a test dose should not be a requirement, it may be recommended for certain high-risk patients. Furthermore, detailed instructions and training for patient and caregiver should be required and included in a medication guide. A "training device" that is identical to the treatment device may be warranted for inclusion in packaging.

9. Advisory Committee Meeting and Other External Consultations

None planned.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Clinical Review
Emily R. Freilich, MD
NDA 211321 Nayzilam (Intranasal midazolam)

The label has not been finalized at the time of this review. See final approved labeling.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

None required.

12. Postmarketing Requirements and Commitments

None required

13. Appendices

13.1. References

See footnotes throughout.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study P261-401

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>170</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the		

number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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/s/

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