IN AN INTERIM ANALYSIS of long-term safety/ tolerability, repeat dosing of diazepam nasal spray demonstrated a safety/tolerability profile consistent with what may be expected for diazepam, appearing independent of usage frequency. No trends were observed for treatment-emergent adverse events, clinical/ laboratory tests, or olfactory changes with higher usage frequency; nasal irritation was mild and transient.

# Introduction

- Risk factors for seizure clusters include a history of clusters, earlier age of epilepsy onset, intractable epilepsy, and a high seizure frequency<sup>1</sup>
- Rescue therapy for seizure clusters has generally relied on benzodiazepines, and the intranasal route of administration conveys several advantages including<sup>2</sup>:
- Non-invasiveness
- High vascularity with a potential for direct nose-to-brain drug delivery
- Bypass of intestinal/liver metabolism
- Diazepam nasal spray (NRL-1, Valtoco<sup>®</sup>) is a proprietary intranasal formulation of diazepam
- Provides a rapid, non-invasive route of administration
- Intended for use as rescue medication in patients with epilepsy who experience cluster seizures despite stable regimens of antiseizure drugs (ASDs)
- Diazepam nasal spray is formulated with vitamin E and Intravail<sup>®</sup> A3 (n-dodecyl-beta-D-maltoside)
- Vitamin E is used to enhance the nonaqueous solubility of diazepam
- Intravail A3 is a nonionic surfactant that is used as an absorption enhancement agent to promote the increased transmucosal bioavailability of drugs<sup>3</sup>
- Diazepam nasal spray has bioavailability and pharmacokinetics that are similar to rectal diazepam but with less variability<sup>4</sup>
- Diazepam nasal spray had no unexpected adverse events (AEs) across age groups, including in pediatric patients aged 6 years or older<sup>4-6</sup>
- As frequency of diazepam nasal spray use will likely vary among patients, it is also important to determine long-term safety and tolerability after chronic exposure

# Objective

 To evaluate long-term safety and tolerability of diazepam nasal spray among patients defined as having moderate and frequent monthly usage

# Safety and Tolerability of NRL-1, an Intranasal Formulation of Diazepam, in Relationship to Usage Frequency in Subjects With Epilepsy: Interim Results From a Phase 3, Open-label, Repeat Dose Study

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# Methods

- This phase 3, repeat dose, open-label study evaluated the safety of diazepam nasal spray in epilepsy subjects who, in the opinion of the investigator, may need benzodiazepine intervention for seizure control at least 1 time every other month on average (ie, average 6 times a year)
- Received institutional review board approval
- Conducted in accordance with Declaration of Helsinki
- All patients or their legal representative provided written informed consent
- This interim analysis (data cutoff as of February 8, 2019) evaluated safety and tolerability stratified by frequency of use based on average number of doses/month
- Moderate use was defined as 1–2 doses/month
- Frequent use was defined as >2 doses/month
- Inclusion criteria:
- Males or females between ages 6 and 65 years, inclusive – Diagnosis of partial or generalized epilepsy with motor seizures or seizures
- with clear alteration of awareness
- Occurrence of seizures despite a stable ASD regimen
- Availability of a qualified caregiver or medical professional who could administer study medication in the event of a seizure
- No clinically significant abnormal findings in their medical history, or on physical examination, electrocardiogram (QTcF <450 msec for males and QTcF <470 msec for females), or clinical laboratory results during screening – Female subjects of childbearing potential agreed to use an approved
- method of birth control
- Key exclusion criteria:
- History of major depression or a past suicide attempt or suicide ideation History of allergy or adverse response to diazepam
- A history of a clinically significant medical condition that would jeopardize the safety of the subject
- Subjects and caregivers were trained on the proper use of the nasal sprayer device at screening and as needed during treatment
- During patient follow-up of approximately 1 year, diazepam nasal spray was administered at 5, 10, 15, or 20 mg (weight-based), with a second dose administered, if needed, 4–12 hours later – Investigators could adjust doses for efficacy or safety
- (TEAEs), physical/neurological examination, vital signs, and laboratory tests
- Safety was evaluated based on incidence of treatment-emergent AEs Tolerability assessments included olfactory changes on the NIH Toolbox Odor Identification Test<sup>7</sup> and nasal irritation measured objectively on the following 6-point scale<sup>8</sup>:
- 0–No sign of nasal irritation or mucosal erosion
- 1A–Focal nasal mucosal irritation or Inflammation
- 1B–Superficial mucosal erosion
- 2–Moderate mucosal erosion
- 3–Ulceration
- 4–Septal perforation

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# **Outcomes/Evaluation Results**

Table 1. Demographic Characteristics, Follow-Up Duration, and Seizure Episodes

Variable	Total (N=132)	Moderate Use, 1–2 Doses/ Month (n=65)	Frequent Use, >2 Doses/ Month (n=67)
Age, years, mean±SD (range)	25.7±15.1 (6–65)	25.5±15.0	25.9±15.3 (6–65)
Sex, n (%)			
Male	61 (46.2)	31 (47.7)	30 (44.8)
Female	71 (53.8)	34 (52.3)	37 (55.2)
Race, n (%)			
White	109 (82.6)	53 (81.5)	56 (83.6)
Black/African-American	12 (9.1)	5 (7.7)	7 (10.4)
Asian	3 (2.3)	2 (3.1)	1 (1.5)
Native Hawaiian or other Pacific Islander	5 (3.8)	3 (4.6)	2 (3.0)
Other	3 (2.3)	2 (3.1)	1 (1.5)
Weight, kg, mean ± SD	65.3±33.8	64.2±31.6	66.4±36.0
Follow-up, months, median	10.8	10.3	11.0
Number of diazepam nasal spray treated seizure episodes	2274	427	1847

- A total of 132 patients were enrolled, administered diazepam nasal spray, and were included in the safety analysis with a median follow-up of 10.8 months (**Table 1**)
- These patients were mostly female (53.8%), white (82.6%), and with a mean age of 25.7 years
- Among these patients, 2274 seizure episodes were treated with diazepam nasal spray; 191 episodes (8.4%) required a second dose
- Monthly use of diazepam nasal spray was moderate in 65 patients (49.2%) and frequent in 67 patients (50.8%) (**Table 1**)
- Age, race, and sex were generally similar in the moderate and frequent use subgroups

#### Figure 1. Retention Rate Kaplan-Meier Plot



Event=1 when subject discontinued; otherwise, event=0

• At the time of this subgroup analysis, the study retention rate (**Figure 1**) was 85.6%

#### Table 2. Treatment-Emergent Adverse Events (TEAEs) by Frequency of Diazepam Nasal Spray Use

	Incidence, n (%)		
TEAEs	Total (N=132)	Moderate Use, 1–2 Doses/ Month (n=65)	Frequent Use, >2 Doses/ Month (n=67)
Any TEAE	91 (68.9)	40 (61.5)	51 (76.1)
TEAEs leading to study discontinuation	1 (0.8)	0	1 (1.5)
Serious TEAEs	37 (28.0)	18 (27.7)	19 (28.4)
Most common TEAEs (≥5% i	n either usa	де дгоир)	
Seizure	17 (12.9)	10 (15.4)	7 (10.4)
Nasopharyngitis	8 (6.1)	2 (3.1)	6 (9.0)
Influenza	7 (5.3)	2 (3.1)	5 (7.5)
Nasal discomfort	7 (5.3)	3 (4.6)	4 (6.0)
Upper respiratory tract infection	7 (5.3)	4 (6.2)	3 (4.5)
Headache	6 (4.5)	1 (1.5)	5 (7.5)
Ругехіа	6 (4.5)	2 (3.1)	4 (6.0)
Dizziness	5 (3.8)	4 (6.2)	1 (1.5)
Contusion	4 (3.0)	0 (0.0)	4 (6.0)
<b>Treatment-related TEAEs</b>	22 (16.7)	7 (10.8)	15 (22.4)
Most common treatment-re	lated TEAEs	(≥2% in either u	sage group)
Nasal discomfort	7 (5.3)	3 (4.6)	4 (6.0)
Headache	4 (3.0)	1 (1.5)	3 (4.5)
Epistaxis	3 (2.3)	1 (1.5)	2 (3.0)
Rhinalgia	2 (1.5)	0 (0.0)	2 (3.0)

- Overall, 91 patients (68.9%) had TEAEs (**Table 2**)
- The incidence of TEAEs was numerically higher with frequent (76.1%) relative to moderate use (61.5%)
- The one TEAE-related discontinuation (major depression and anxiety) was in a frequent user; this TEAE was not treatment-related
- 37 patients (28.0%) had serious TEAEs, none of which were deemed related to treatment
- The most common TEAEs generally had a numerically higher incidence among frequent users relative to moderate users (Table 2)
- There were relatively few treatment-related TEAEs overall, these events were transient, and the most common had an incidence that was numerically higher in frequent users (Table 2)
- No clinically relevant trends were observed for usage frequency effects on clinical or laboratory parameters

### Table 3. Nasal Irritation

	Number (%) of Patients With Data at Each Time Point			
Time Point	Moderate Use, 1–2 Doses/ Month (n=65)	Frequent Use, >2 Doses/ Month (n=67)		
Baseline, n	41	61		
0–No sign of nasal irritation or mucosal erosion	39 (95.1)	59 (96.7)		
1A–Focal nasal mucosal irritation or Inflammation	2 (4.9)	2 (3.3)		
Day 30, n	41	59		
0–No sign of nasal irritation or mucosal erosion	41 (100)	58 (98.3)		
1A–Focal nasal mucosal irritation or Inflammation	0	1 (1.7)		
Day 90, n	34	60		
0–No sign of nasal irritation or mucosal erosion	34 (100)	58 (96.7)		
1A–Focal nasal mucosal irritation or Inflammation	0	2 (3.3)		
Day 150, n	29	53		
0–No sign of nasal irritation or mucosal erosion	28 (96.6)	52 (98.1)		
1A–Focal nasal mucosal irritation or Inflammation	1 (3.4)	0		
1B–Superficial mucosal erosion	0	1 (1.9)		
Day 210, n	24	48		
0–No sign of nasal irritation or mucosal erosion	24 (100)	48 (100)		
Day 270, n	20	44		
0–No sign of nasal irritation or mucosal erosion	20 (100)	43 (97.7)		
1A–Focal nasal mucosal irritation or Inflammation	0	1 (2.3)		
Day 330, n	17	27		
0–No sign of nasal irritation or mucosal erosion	17 (100)	25 (92.6)		
1A–Focal nasal mucosal irritation or Inflammation	0	1 (3.7)		
1B–Superficial mucosal erosion	0	1 (3.7)		
Day 365, n	12	28		
0–No sign of nasal irritation or mucosal erosion	12 (100)	28 (100)		
• The few reports of pasal irritation were mild (maximum				

- The rew reports of hasal initiation were mild (maximum grade 1B, superficial mucosal erosion), and had a slightly higher incidence in frequent users (**Table 3**)
- Smell tests showed minimal olfactory changes that did not appear to be related to usage frequency (data not shown)

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## Conclusion/Nursing Implications

Diazepam nasal spray provides a rapid, noninvasive route to administer rescue medications for cluster seizures. One hundred thirty-two patients on stable doses of ASDs had a total of 2247 cluster seizures. Of the 2274 seizure episodes, 191 (8.4%) required a second dose. Overall, diazepam nasal spray demonstrated favorable long-term safety and tolerability for patients, with an increased incidence of TEAEs noted primarily in frequent users. The safety and tolerability with all doses was favorable with few incidences of nasal irritation or olfactory complications identified. Moreover, the safety and tolerability is what would be expected for diazepam. Informing patients and their care partners of the patients' experience in the clinical trial will be important to both prepare them for what to expect with using diazepam nasal spray. Combined with ease of use, nurses can feel confident administering the medication and teaching care partners to use it.

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