POSTER
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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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Background

- Risk factors for seizure clusters include a history of clusters, earlier age of epilepsy onset, intractable epilepsy, and a high seizure frequency[1]
- Rescue therapy for seizure clusters has generally relied on benzodiazepines, and the intranasal route of administration conveys several advantages including[2]:
  - Non-invasiveness
  - High vascularity with a potential for direct nose-to-brain drug delivery
  - Bypass of intestinal/liver metabolism
- Diazepam nasal spray (Valtoco®, NRL-1) is a proprietary intranasal formulation of diazepam
  - Provides a rapid, non-invasive route of administration
- Indicated for the short-term treatment of seizure clusters in patients 6 years of age and older
- Diazepam nasal spray is formulated with vitamin E and Intravail® 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[3]
- Diazepam nasal spray has bioavailability and pharmacokinetics that are similar to rectal diazepam but with less variability[4]
- Diazepam nasal spray had no unexpected adverse events (AEs) across age groups, including in pediatric patients aged 6 years or older[4-6]
- 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

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 antiseizure-drug (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
- Safety was evaluated based on incidence of treatment-emergent AEs (TEAEs), physical/neurological examination, vital signs, and laboratory tests
- Tolerability assessments included olfactory changes on the NIH Toolbox Odor Identification Test[7] and nasal irritation measured objectively on the following 6-point scale[8]:
  - 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

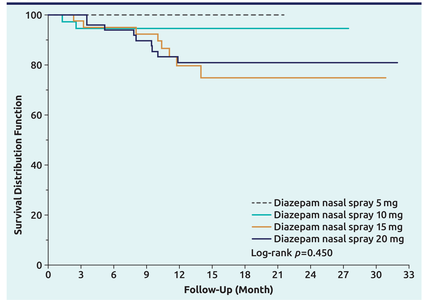
Results

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 (**Table 1**)
  - Among these patients, 2274 seizure episodes were treated with diazepam nasal spray; 191 episodes (8.5%) required a second dose
- Monthly use of diazepam nasal spray was moderate in 65 patients (49.2%) and frequent in 67 patients (50.8%)
  - 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

TEAEs	Incidence, n (%)		
	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% in either usage group)			
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)
Pyrexia	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)
Treatment-related TEAEs	22 (16.7)	7 (10.8)	15 (22.4)
Most common treatment-related TEAEs (≥2% in either usage 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

Time Point	Number (%) of Patients With Data at Each 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	52
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 nasal irritation 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)

Conclusions

- In this interim analysis among 132 patients with 2247 seizure episodes despite stable regimens of ASDs, diazepam nasal spray demonstrated favorable long-term safety and tolerability with repeat dosing
  - Retention rate was high
- The safety/tolerability profile by usage frequency appeared to be generally similar between usage groups, with slightly higher TEAE rates in patients with more frequent use
  - No new safety concerns were identified, and no trends were observed for TEAEs, clinical/laboratory tests, or olfactory changes with higher usage frequency
  - Nasal irritation was mild and transient
- The overall safety/tolerability profile of diazepam nasal spray was consistent with what may be expected for diazepam

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