Abstract Description

Self-administration of diazepam nasal spray (VALTOCO®) for seizure clusters represents a possible benefit over routes requiring a care partner. Nearly half of surveyed patients self-administering in this phase 3 study reported dosing primarily at the first signs a cluster was coming. This suggests patients took steps to self-control their treatment.

Characteristics of Patients Who Self-Administered Diazepam Nasal Spray for Seizure Clusters: Interim Results From a Phase 3, Open-Label, Repeat-Dose Safety Study

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Introduction

- Some patients with epilepsy may experience seizure clusters despite the use of a stable regimen of antiseizure drugs[1,2]
- Seizure clusters can have a negative impact on patient quality of life as well as adding emotional and economic burdens for both patients and care partners[2]
- Rectal diazepam has been used as a rescue therapy for the treatment of seizure clusters for more than 20 years[1]
  - However, many patients and care partners have concerns about the social acceptability of this route of administration, particularly in the community setting, and rectal diazepam may have substantial intrapatient variability in bioavailability[2,3]
- Diazepam nasal spray (Valtoco®), formulated with Intravail® A3, was recently approved by the US Food and Drug Administration for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) in patients with epilepsy aged 6 years or older,[4] is designed to provide a rapid, noninvasive, and socially acceptable route of administration for the treatment of seizure clusters
  - It has shown rapid absorption and comparable bioavailability to rectal diazepam with less intrapatient variability[3]
  - The potential for self-administration of diazepam nasal spray may provide patients with more control

Objective

- Survey responses from patients enrolled in a long-term safety study of diazepam nasal spray and who reported self-administering their treatment were examined to analyze patient perceptions of rescue therapy for seizure clusters

Methods

Study Design and Patients

- This phase 3, repeat-dose, open-label safety study of diazepam nasal spray (NCT02721069) enrolled patients with epilepsy who were expected to need benzodiazepine treatment for seizure control
- Key inclusion criteria
  - Male or female patients aged 6–65 years
  - Diagnosis of either partial or generalized epilepsy with motor seizures or seizures with clear alteration of awareness
    - History of status epilepticus or allergic rhinitis and current concomitant benzodiazepine use were permitted
  - Availability of a qualified care partner or medical professional to administer study medication in the event of a seizure
  - No clinically significant abnormal findings in the patient's medical history, or on physical examination, electrocardiogram, or clinical laboratory results during screening
  - Female patients of childbearing potential were required to use an approved method of birth control
- Key exclusion criteria
  - History of major depression or a past suicide attempt or suicidal ideation
  - History of allergy or adverse response to diazepam
  - History of a clinically significant medical condition that would jeopardize the safety of the patient

Treatment

- Patients and care partners were trained to administer diazepam nasal spray in doses of 5, 10, 15, or 20 mg, based on patient age and weight; a second dose was administered 4–12 hours after the first dose if needed

Survey Design

- Patient surveys were given at one time point, near study end, to be returned at the next visit, and were mailed to patients who had already completed or discontinued the study
  - Surveys were developed by the study investigators and an expert panel of epileptologists treating adult or pediatric patients
  - Questions assessed various facets of patients' experiences, including comfort using diazepam nasal spray outside the home, timing of administration and return to their usual selves, and convenience of use compared with rectal diazepam
  - Surveys were provided in paper format with true/false or multiple-choice questions; responses were subsequently entered into the database
  - Respondents were not required to answer every question
- Responders received nominal compensation ($50) for their time
- Patient safety was assessed and reported as treatment-emergent adverse events (TEAEs)

Results

Patient Demographics

- A total of 175 patients were enrolled in the study; of these, 158 received at least 1 dose of study treatment
- As of the October 31, 2019, interim cutoff date, 67 treated patients had returned the survey; 66 also had seizure diary data and were included in the demographic and safety analysis
- Of these, 27 reported self-administration of diazepam nasal spray (**Table 1**)
  - Median age of patients who self-administered diazepam nasal spray was 34.0 years; patient ages ranged from 11–65 years

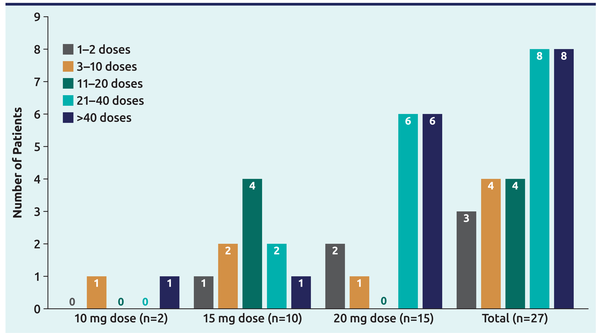
Table 1. Patient Characteristics (n=27)

Characteristic, n (%)	Diazepam Nasal Spray			Total* (n=27)
	10 mg (n=2)	15 mg (n=10)	20 mg (n=15)	
Age, y, median (range)	38.0 (11–65)	25.5 (16–54)	38.0 (22–59)	34.0 (11–65)
Sex				
Male	1 (50.0)	5 (50.0)	6 (40.0)	12 (44.4)
Female	1 (50.0)	5 (50.0)	9 (60.0)	15 (55.6)
Race				
White	1 (50.0)	8 (80.0)	13 (86.7)	22 (81.5)
Black or African American	0	1 (10.0)	0	1 (3.7)
Asian	1 (50.0)	0	0	1 (3.7)
Native Hawaiian/other Pacific Islander	0	0	1 (6.7)	1 (3.7)
Other	0	1 (10.0)	1 (6.7)	2 (7.4)
Duration of exposure				
6–<12 mo	0	1 (10.0)	0	1 (3.7)
≥12 mo	2 (100.0)	9 (90.0)	15 (100.0)	26 (96.3)

*No patients reporting self-administration received the 5-mg dose.

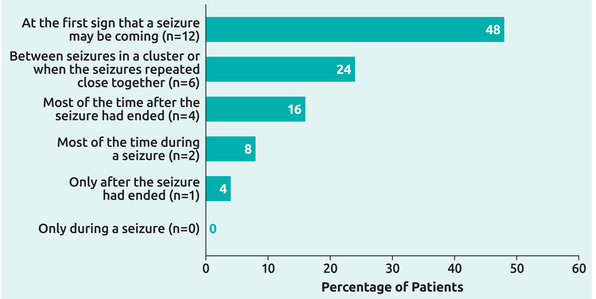
- Most patients (26/27; 96.3%) had a duration of use of diazepam nasal spray ≥12 months
- A total of 994 doses were administered (by the patients or their care partners) in this subgroup of 27 patients: 10 mg, n=61 (6.1%); 15 mg, n=180 (18.1%); and 20 mg, n=753 (75.8%)
  - The rate of dosing errors was low (11/994 [1.1%])
- Of the 27 patients who self-administered doses, 3 (11.1%) administered 1–2 doses, 4 (14.8%) administered either 3–10 or 11–20 doses, and 8 (29.6%) administered either 21–40 or >40 doses (**Figure 1**)

Figure 1. Number of Doses of Diazepam Nasal Spray Self-Administered by Patients (n=27)



- Of the patients who self-administered diazepam nasal spray and responded to the timing questions, 12/25 (48%) reported primarily administering a dose at the first sign that a seizure may be coming (**Figure 2**)
- Twenty-one respondents (77.8%) reported that self-administration of diazepam nasal spray was either very (n=10) or extremely (n=11) easy
- The majority of patients (n=19; 70.4%) reported that self-administering diazepam nasal spray in a public setting was either somewhat (n=11), very (n=4), or extremely (n=5) comfortable

Figure 2. Primary Timing of Administration of Diazepam Nasal Spray by Patients Who Self-Administered Doses (n=25)



Safety

- TEAEs were reported in 20 patients (74.1%)
  - Six patients (22.2%) had a TEAE that was possibly treatment related; nasal discomfort was the only one reported in >2% of patients (n=4, 14.8%)
    - Nasal discomfort was mild (n=3) or moderate (n=1) and transient
- Six patients reported a serious TEAE; none were considered treatment related

Conclusions

- Twenty-seven patients who were enrolled in a phase 3 repeat-dose safety study of diazepam nasal spray reported on an exit survey that they self-administered diazepam nasal spray in a manner consistent with the prescribing information
  - This represents a possible benefit compared with other routes of administration that require care partner administration
- Patients reported that diazepam nasal spray was easy to administer
- Patient responses suggest that they were taking steps to self-control their treatment
  - Nearly half of the patients reported administering diazepam nasal spray at the first signs that a seizure was coming
- The safety profile in these patients was consistent with what has been reported for diazepam
- Safety results were consistent with the overall results observed in the study and with the results of all patients who responded to the survey
- Nasal discomfort was present in 15% of patients and was mostly mild and transient

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Disclosures **Dr Cook** is an employee of and has received stock options from Neurelis, Inc. **Dr Penovich** has served on speakers bureaus for GW Pharmaceuticals; Greenwich Biosciences; Neurelis, Inc.; SK Life Sciences; and UCB, and is an advisor to Engage Therapeutics; Neurelis, Inc.; and SK Life Sciences. **Dr Wheless** has served as an advisor or consultant for CombiMatrix; Eisai, Inc.; GW Pharmaceuticals; Lundbeck, Inc.; Neurelis, Inc; NeuroPace, Inc.; Supernus Pharmaceuticals, Inc.; and Upsher-Smith Laboratories, Inc. Dr Wheless has served as a speaker or a member of a speakers bureau for Cyberonics, Inc.; Eisai, Inc.; Lundbeck, Inc.; Mallinckrodt; Neurelis, Inc.; Supernus Pharmaceuticals, Inc.; Upsher-Smith Laboratories, Inc., and has received grants for clinical research from Acorda Therapeutics; GW Pharmaceuticals; Insys Therapeutics, Inc.; Lundbeck, Inc.; Mallinckrodt; Neurelis, Inc.; NeuroPace, Inc.; Upsher-Smith Laboratories, Inc.; and Zogenix, Inc. **Dr Hogan** has received research support from UCB Pharmaceuticals, Neurelis, Inc; and Biogen Inc, and is an advisor for Neurelis, Inc. **Ms Guerra** and **Dr Rabinowicz** are employees of and have received stock options from Neurelis, Inc. **Dr Carrazana** is an employee of and has received stock and stock options from Neurelis, Inc. Dr Carrazana has received compensation for serving on the boards of directors of Marinus and Hawaii-Biotech.

References **1.** Haut SR. *Curr Opin Neurol.* 2015;28(2):143-150. **2.** Penovich PE, et al. *Neurologist.* 2017;22(6):207-214. **3.** Hogan RE, et al. *Epilepsia.* 2020;61(3):455-464. **4.** Neurelis, Inc. VALTOCO® (diazepam nasal spray). Full Prescribing Information. Neurelis, Inc.; 2020.

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