POSTER
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Effectiveness and Safety of Valtoco® (NRL-1; diazepam nasal spray) in Patients With Epilepsy and a History of Seasonal Allergies: Interim Results From a Phase 3, Open-Label, 12-Month Repeat Dose Study

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Background

- The intranasal route of drug administration may present challenges due to nasal anatomy and physiology, such as limited volume, residence time, and absorption[1]
  - One such challenge is the possibility of variable absorption due to such conditions as colds and allergies[1]
- Per the literature, seasonal allergies and nasal congestion do not affect intranasal administration of agents such as testosterone and fentanyl[2,3]
  - However, for patients with epilepsy experiencing seizure clusters, it is important to determine whether this lack of impact also extends to the safety and effectiveness of intranasal rescue therapy
- Benzodiazepines are considered the mainstay of rescue therapy for seizure clusters,[4] but they may have limited absorption due to low water solubility[1]
- Diazepam nasal spray (Valtoco®, NRL-1) is a unique intranasal formulation of diazepam formulated with Intravail® A3 (n-dodecyl-beta-D-maltoside) and vitamin E, indicated for the short-term treatment of seizure clusters in patients 6 years of age and older
  - Intravail A3 is a nonionic surfactant that is used as an absorption enhancement agent to promote the increased transmucosal bioavailability of drugs[5]
  - Vitamin E is used to enhance the non-aqueous solubility of diazepam

Objective

- This analysis evaluated the impact of a patient's history of seasonal allergies on the safety and doses needed per episode of diazepam nasal spray as rescue medication in patients with epilepsy who experience seizures despite stable regimens of antiseizure drugs (ASDs)

Methods

- Results are from an interim analysis (data cutoff as of February 8, 2019) of an ongoing, phase 3, repeat dose, open-label, safety study of diazepam nasal spray
  - Received institutional review board approval
  - Conducted in accordance with Declaration of Helsinki
  - Written informed consent was provided for all subjects
- Enrolled patients were those with epilepsy who were expected to need benzodiazepine treatment for seizure control once every other month on average (ie, average 6 times a year) despite a stable regimen of ASDs
  - Males or females aged between 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
- Caregivers administered 5, 10, 15, or 20 mg of diazepam nasal spray (weight-based), with a second dose administered, if needed, 4–12 hours later
  - Investigators could adjust doses for efficacy/safety
- The proportion of seizure events that did not require a second dose of diazepam nasal spray was measured in a post hoc analysis
- Safety measures included treatment-emergent adverse events (TEAEs), physical/neurological examination, vital signs, laboratory tests
- This subgroup analysis evaluated patients with or without a positive past medical history of seasonal allergies

Results

Table 1. Demographic Characteristics (N=132)

Variable	Allergic History (n=27)	No Allergic History (n=105)
Age, years, mean ± SD (range)	25.2±4.7 (6–53)	25.8±15.3 (6–65)
Sex, n (%)		
Male	17 (63.0)	44 (41.9)
Female	10 (37.0)	61 (58.1)
Race, n (%)		
White	19 (70.4)	90 (85.7)
Black/African-American	6 (22.2)	6 (5.7)
Asian	0	3 (2.9)
Native Hawaiian or other Pacific Islander	2 (7.4)	3 (2.9)
Other	0	3 (2.9)
Allergy type, n (%)		
Seasonal	21 (77.8)	—
Rhinitis	4 (14.8)	—
Allergy/Chronic sinus infection	1 (3.7)	—
Respiratory allergy	1 (3.7)	—

- The safety population of the interim analysis consisted of 132 patients aged 6 to 65 years (53.8% female, 82.6% white, mean age 25.7±15.1 years)
- A history of allergies was present in 27 patients (20.5%) aged 6 to 53 years of whom 37.0% were female and 70.4% were white (**Table 1**)
- Seasonal allergies were the most common type of allergy (77.8%) (**Table 1**)
  - All but 1 patient had ongoing allergies

Table 2. Duration of Exposure and Seizure Episodes (N=132)

Variable	Allergic History (n=27)	No Allergic History (n=105)
Duration of exposure, n (%)		
<6 months	1 (3.7)	17 (16.2)
6 to <12 months	12 (44.4)	35 (33.3)
≥12 months	14 (51.9)	53 (50.5)
Patients requiring ≥2 doses/month, n (%)	15 (55.6)	62 (59.0)
Number of diazepam nasal spray treated seizure episodes	428	1838
Seizure episodes requiring a second dose, n (%)	14 (3.3)	177 (9.6)

- Approximately half of the patients in both subgroups had a duration of exposure of at least 12 months (**Table 2**)
- In both subgroups, the majority of patients averaged ≥2 doses per month (**Table 2**)
- Patients with a history of allergy experienced 428 seizure episodes that were treated with diazepam nasal spray, of which 14 episodes (3.3%) required a second dose of medication (**Table 2**)
  - In the subgroup without an allergic history, 177 (9.6%) of the 1838 seizure episodes treated with diazepam nasal spray required a second dose

Table 3. Treatment-Emergent Adverse Events (TEAEs)

TEAE	Allergic History (n=27)	No Allergic History (n=105)
Any TEAE	19 (70.4)	72 (68.6)
Serious TEAE	7 (25.9)	30 (28.6)
Treatment-related TEAE	3 (11.1)[a]	19 (18.1)
Most common TEAEs (≥5% in either subgroup)		
Pneumonia	3 (11.1)	3 (2.9)
Pyrexia	3 (11.1)	3 (2.9)
Seizure	3 (11.1)	14 (13.3)
Sinusitis	3 (11.1)	1 (1.0)
Anxiety	2 (7.4)	0
Ear infection	2 (7.4)	0
Nasopharyngitis	2 (7.4)	6 (5.7)
Somnolence	2 (7.4)	4 (3.8)
Upper respiratory tract infection	2 (7.4)	5 (4.8)
Influenza	0	7 (6.7)
Nasal discomfort	NR	7 (6.7)

[a]Specific treatment-related adverse events are provided in the text.
NR, not reported.

- In the subgroup of patients with a history of allergies, 19 (70.4%) had TEAEs (**Table 3**)
  - 7 patients (25.9%) had serious TEAEs, none of which were deemed treatment-related
  - 3 patients (11.1%) had TEAEs that were considered treatment-related (headache, somnolence, sleep disorder, and eye irritation)
- In the group of patients without a history of seasonal allergies, 72 (68.6%) had TEAEs (**Table 3**)
  - 30 patients (28.6%) had serious TEAEs and 19 (18.1%) had treatment-related TEAEs
- The most common TEAEs were generally similar in both groups (**Table 3**)
- There were no clinically relevant trends in effects on vital signs or laboratory tests, and no electrocardiographic abnormalities were observed

Conclusions

- In this interim analysis of long-term safety of treatment with diazepam nasal spray, the presence of seasonal allergies had no impact on the number of diazepam nasal spray doses needed for a seizure-cluster episode
- In subgroups of patients with and without allergies, repeated dosing of diazepam nasal spray demonstrated a similar safety/tolerability profile

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