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Time of Day of Occurrence of Seizure Clusters in Patients With Epilepsy Treated With Diazepam Nasal Spray: Interim Results From a Phase 3, Open-Label, Repeat-Dose Safety Study

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Background

- Many types of epilepsy have a diurnal component, and the autonomic nervous system and chronobiology are factors in drug-resistant epilepsy[1]
- Diurnal seizure patterns may provide important information for improving aspects of patient care ranging from seizure control and quality of life to sudden unexpected death in epilepsy[2,3]
  - Seizures have been reported to occur in specific circadian patterns and sleep/wake distributions depending on seizure type and onset location[1,2]
- A study using online diaries from 1177 patients with seizure clusters (also called acute repetitive seizures) characterized patterns of occurrence of more than 1 seizure over a 24-hour period[4]
  - However, there are few time-of-day data for patients with seizure clusters
- Benzodiazepines are the cornerstone of treatment for seizure clusters[5,6]
- Diazepam nasal spray (Valtoco®), formulated with Intravail® A3 (n-dodecyl-beta-D-maltoside) and vitamin E, is a proprietary intranasal formulation of diazepam 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[7]

Objective

- A hypothesis-generating time-of-day analysis of seizure onset was conducted using data from an interim cutoff of a long-term, repeat-dose safety study of diazepam nasal spray

Methods

- The results presented here are from an interim analysis (data cutoff October 31, 2019) of a phase 3, open-label, repeat-dose safety study of diazepam nasal spray
  - Study received institutional review board approval
  - Study was conducted in accordance with the Declaration of Helsinki
  - Written informed consent was obtained for all participants
- Enrolled patients were those with epilepsy who were expected to need benzodiazepine treatment for seizure control once every other month on average (ie, average of 6 times a year) despite a stable regimen of antiseizure drugs
- Key inclusion criteria
  - Male or female patients aged 6–65 years
  - Diagnosis of partial or generalized epilepsy with motor seizures or seizures with clear alteration of awareness
  - Availability of a qualified care partner 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, or clinical laboratory results during screening
  - Female patients 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 suicidal ideation
  - History of allergy or adverse response to diazepam
  - A history of a clinically significant medical condition that would jeopardize the safety of the patient

Treatment

- Patients and care partners were trained on the proper use of the nasal sprayer device at screening and as needed during treatment
- Care partners or patients administered diazepam nasal spray (age and weight based), with a second dose 4–12 hours later if needed
  - For patients 6–11 years of age, dosing was 5 mg (10–18 kg patient weight), 10 mg (19–37 kg), 15 mg (38–55 kg), or 20 mg (56–74 kg)
  - For patients 12 years of age and older, dosing was 5 mg (14–27 kg patient weight), 10 mg (28–50 kg), 15 mg (51–75 kg), or 20 mg (≥76 kg)
  - Investigators could adjust doses if a different dose was necessary per their medical judgment and if there were no safety concerns associated with the dosing change

Analysis

- Seizures, doses, and time of administration were recorded in a diary
  - In this analysis, clock time of onset of each seizure episode was assessed
- Safety measures included assessment of treatment-emergent adverse events (TEAEs)
- Data were summarized with descriptive statistics

Results

- At the October 31, 2019, interim cutoff, 175 patients were enrolled; 158 had been treated with diazepam nasal spray and were included in the safety population (**Table 1**)

Table 1. Baseline Demographics (Safety Population, n=158)

	Dose				
	5 mg (n=8)[a]	10 mg (n=52)	15 mg (n=45)	20 mg (n=53)	Total (n=158)
Age, y, mean±SD (range)	9.6±6.93 (6–26)	12.1±9.16 (6–65)	27.6±13.73 (10–59)	33.4±13.03 (11–59)	23.5±15.13 (6–65)
Weight, kg, mean±SD (range)	18.7±4.82 (12–27)	31.5±12.17 (19–86)	60.8±9.08 (36–78)	96.3±28.10 (34–221)	60.9±33.66 (12–221)
Sex, n (%)					
Male	2 (25.0)	27 (51.9)	15 (33.3)	29 (54.7)	73 (46.2)
Female	6 (75.0)	25 (48.1)	30 (66.7)	24 (45.3)	85 (53.8)

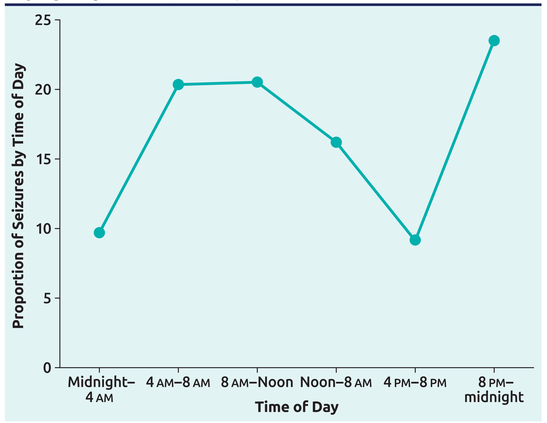
[a]n=number of patients.

- Duration of exposure was ≥12 months in 116 patients (73.4%), 6–<12 months in 31 patients (19.6%), and <6 months in 11 patients (7.0%)
  - Eighty-nine patients (56.3%) averaged ≥2 doses per month
  - At the interim analysis, the retention rate was 82.9%

Seizures

- Start dates and times were reported for 3646 seizures (**Figure 1**)
  - Onset was generally highest during mornings and late evenings
  - Onset was generally lowest in the afternoon, early evening, and middle of the night

Figure 1. Time of Day of Seizure Occurrence (All Doses; Safety Population; n=158)



- The pattern was generally consistent across dosing groups, with some apparent variation in the 5- and 10-mg groups (**Table 2**)

Table 2. Time of Day of Seizure Occurrence by Diazepam Nasal Spray Dose Group (Safety Population; n=158)

	Dose				
Seizure Cluster Start Time, n[a] (%)	5 mg (n=137)	10 mg (n=1013)	15 mg (n=922)	20 mg (n=1574)	Total (N=3646)
Midnight–4 AM	4 (2.9)	114 (11.3)	52 (5.6)	185 (11.8)	355 (9.7)
4 AM–8 AM	12 (8.8)	329 (32.5)	123 (13.3)	278 (17.7)	742 (20.4)
8 AM–noon	20 (14.6)	210 (20.7)	184 (20.0)	335 (21.3)	749 (20.5)
Noon–4 PM	27 (19.7)	130 (12.8)	176 (19.1)	261 (16.6)	594 (16.3)
4 PM–8 PM	19 (13.9)	77 (7.6)	106 (11.5)	136 (8.6)	338 (9.3)
8 PM–midnight	54 (39.4)	152 (15.0)	278 (30.2)	373 (23.7)	857 (23.5)
Time not reported	1 (0.7)	1 (0.1)	3 (0.3)	6 (0.4)	11 (0.3)

[a]n=number of seizures with reported start times.

Safety

- TEAEs were reported for 119 patients (75.3%; **Table 3**), with 6 (3.8% of the safety population) in the 5-mg group, 38 (24.1%) in the 10-mg group, 34 (21.5%) in the 15-mg group, and 41 (25.9%) in the 20-mg group; none were unexpected for diazepam
- There were no discontinuations due to a TEAE
- The most common treatment-related AEs were nasal discomfort (5.7%) and headache (2.5%)

Table 3. Summary of TEAEs (Safety Population; n=158)

TEAE Incidence, n[a] (%)	Total (n=158)
≥1 TEAE	119 (75.3)
TEAE leading to discontinuation	0
Serious TEAE	45 (28.5)
Treatment-related TEAE	26 (16.5)
Most common TEAEs (≥5% of all patients)	
Seizure	23 (14.6)
Nasopharyngitis	12 (7.6)
Upper respiratory tract infection	12 (7.6)
Pneumonia	11 (7.0)
Pyrexia	10 (6.3)
Nasal discomfort	9 (5.7)
Influenza	8 (5.1)

TEAE=treatment-emergent adverse event.
[a]n=number of patients.

Conclusions

- These preliminary results confirm previous results suggesting a circadian pattern of seizures, which has implications for monitoring individual patients and for potential administration of antiseizure drugs and intermittent rescue treatment at specific individual time points to break the cycle of their seizure clusters
  - In this study, dose groups corresponded to patient weight and age; however, small numbers limit interpretation in the lowest dose group
- Diazepam nasal spray safety was consistent with the established profile of diazepam
- Further analysis of seizure patterns by seizure type and other variables is warranted upon study completion; a machine learning approach could be useful for defining how many patterns exist

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