Final results from a phase 3, long-term, safety study of diazepam nasal spray for seizure clusters in patients with epilepsy

Narrator: [0:00] This podcast is presented and supported by Neurelis, Inc. It is provided for informational purposes only and is not intended to replace a discussion with a healthcare provider. All decisions regarding patient care must be made with a healthcare provider and consider the unique characteristics of each patient. This podcast discusses Valtoco® (diazepam nasal spray).Valtoco is indicated for the acute treatment of intermittent of stereotypic episodes of frequent seizure activity, also known as seizure clusters or acute repetitive seizures, that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.

Here is some important safety information for Valtoco.

Warning: Risks from Concomitant Use with Opioids; Abuse, Misuse, and Addiction, and Dependence and Withdrawal reactions. Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

The use of benzodiazepines, including Valtoco, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing Valtoco and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.

The continued use of benzodiazepines may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Although Valtoco is indicated only for intermittent use, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of Valtoco may precipitate acute withdrawal reactions, which can be life-threatening. For patients using Valtoco more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue Valtoco.

Please listen to additional important safety information for Valtoco presented at the end of this podcast.

Narrator: [2:18] Welcome to the Neurelis Medical Affairs podcast series. These podcasts offer an opportunity to learn directly from the authors about recently published articles discussing strategies for the treatment of seizure clusters in patients with epilepsy. The series can be accessed at NeurelisMedicalAffairs.com or through a Neurelis Medical Science Liaison.

In this episode, we hear from Dr. James Wheless from Le Bonheur Children's Hospital and the University of Tennessee Health Science Center in Memphis. He discusses the final study result of a large, open-label, phase 3 safety study of diazepam nasal spray. The findings were published in 2021 by Wheless and colleagues in the paper, "Final results from a phase 3, long-term, open-label, repeat-dose safety study of diazepam nasal spray for seizure clusters in patients with epilepsy" in the journal *Epilepsia*.

Welcome Dr. Wheless, thank you for joining us today. It is an honor to have you share with us the results of the diazepam nasal spray long-term study you and your colleagues completed and published in 2021.

Wheless: [3:20] Thanks for having me here today.

Narrator: [3:23] To start, Dr. Wheless, perhaps you can explain the need for novel treatments for rescue therapy among patients with epilepsy who have seizure clusters.

Wheless: [3:30] So seizure clusters, or seizures that repeat multiple times in a 24-hour period, represent a seizure emergency. Patients that have these we know are at increased risk of serious difficulties, so they can present to the emergency room. A fixed number can progress to status epilepticus, and at the minimal, it's very disruptive to the patient and their caregiver's life when they would have to stop and address the seizure emergency.

Historically, we know that benzodiazepines have been used to treat seizure emergencies, and that's what's part of our current rescue therapy. In 1997, rectal diazepam was approved, and it's been the only option available for more than two decades. And while this option was available, as clinicians we knew that it was not embraced by all of our patients. There clearly are difficulties to administering a rectal medication. There were significant social obstacles in our older patients as they got into older childhood, adolescence, and adulthood. And even the product itself has significant variability in its pharmacokinetics between patients.

So, these challenges were there, and thankfully, these challenges were addressed and there was approval of two intranasal benzodiazepine treatments, one in 2019 and one in 2020. The FDA-approved indication for diazepam nasal spray is for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (that is, seizure clusters or acute repetitive seizures), and these are events that are distinct from the patient's usual seizure pattern.

The FDA indication is for patients that are aged six years and older with epilepsy. And the diazepam is formulated in a nasal spray that has vitamin E so that it's not irritating to

the nasal mucosa and a proprietary product called Intravail A3 that enhances absorption of the diazepam across the nasal mucosa.

So with that background, the purpose of the present phase three safety study was to evaluate the long-term safety of repeated doses of diazepam nasal spray used as rescue therapy in patients with epilepsy who have frequent seizure clusters—in other words, to really simulate the real-world use of this product in patients that need rescue therapy.

Narrator: [6:04] Thank you. Now, let's turn to the study. Dr. Wheless, please describe the key elements of the study design along with the outcome measures.

Wheless: [6:12] This study was a phase three, open-label, repeat-dose safety study. It was primarily a safety study. Diazepam was known to be effective, but the key was to document the safety of use by this novel route of administration over multiple doses.

So how was this study performed? Patients were identified. The patients or their caregivers were given the intranasal diazepam product, and they were followed over a minimum of 12 months with the possibility of extension for some of the patients.

The dose of the nasal spray was based on the patient age and body weight to make sure that the patients were getting the appropriate or correct dose of the medication for them to use during their seizure emergency. The patients were seen back intermittently during the study. That dose could be adjusted for effectiveness or safety if needed, before the patients left clinic. Initially, both the patients and their caregivers were trained on how to use the nasal spray and were instructed to give it for seizure clusters and that they could repeat, if needed, a second dose 4 to 12 hours after the first dose was given in a given day.

The patients and their caregivers kept a diary. They recorded the seizure onset for the seizure cluster and when they gave intranasal diazepam. And then when patients were seen back in clinic, we asked them about treatment-emergent adverse events related to the use of the product and assessed the possible relationship of any adverse events to the therapy.

We wanted to know, did patients tolerate this medication? So, that included looking at nasal irritation. That was assessed by direct observation at the clinic visits along with a test for olfaction. And then finally, we wanted to look at effectiveness. A proxy measure for effectiveness was used, and the decision was made to look at the number of patients that treated their seizure cluster and then needed a second dose within the 24-hour period that defined the seizure cluster. We measured retention, so did the patients continue with the therapy? And then finally, we looked at two exploratory endpoints for potential signals of benzodiazepine tolerance. And we'll talk about those later.

Narrator: [8:38] Dr. Wheless talked to us about the inclusion and exclusion criteria for the study. Was there anything noteworthy?

Wheless: [8:44] So the study had several unique features that I'll highlight. It was a multicenter study performed in the United States. Twenty-one centers participated. Patients were ages 6 to 65 years, and to enter, they had to have either partial or generalized seizures with a motor component or seizures with a clear alteration of awareness. And the expectation was that these patients coming into the study would have clusters about every other month while being on a stable anti-seizure medication regimen.

Of note particularly, patients were allowed in that had a prior history of status epilepticus. Patients with a history of seasonal allergies or rhinitis were allowed in. And there was no

restriction on concomitant benzodiazepine use, so patients on clobazam were allowed in the study.

And exclusion criteria fit with probably what you would think: if they had a significant medical condition that would jeopardize the safety for them to be in the study, they were excluded. Or if they had a history of major depression, suicidal ideation, or suicide attempt.

Narrator: [9:57] Before we discuss the main study results, perhaps we can cover who joined the study. Can you describe the characteristics of the patients enrolled in the study and their exposure to diazepam nasal spray over the course of the study?

Wheless: [10:08] So there were 175 patients enrolled. Of those, 163 received at least one dose during the study. 117 completed the 12-month study, for a retention rate of approximately 72%.

Remember that patients were allowed in from age 6 to 65 years. Approximately 1/4 of patients were between 6 and 11 years and the mean age was 23.1 years. Participants were split almost evenly female to male, with slightly more females.

The mean duration that patients stayed on intranasal diazepam in this study was almost a year and a half—it was 17.4 months. And slightly over 80% had a duration in the study of 12 months or greater.

This was a large study with a huge number of seizure clusters and treatments administered. There were 3853 seizure clusters recorded. And that resulted in 4390 doses of diazepam nasal spray.

Even with this large number of doses given, dosing errors occurred in less than 1% of doses or only 42 administrations.

As you might guess, these patients were all different and they varied in how often they used their intranasal diazepam. If we look at kind of users, we can see that patients at the lower end, maybe using it once to twice a month, was approximately half. Those using it twice or more a month represented approximately half also. We look at maybe more frequent users, we see that 42% approximately used it two to five times a month, and approximately 5% used it more than five times.

Narrator: [12:02] Interesting, thank you. Safety measures were the primary outcomes of interest in this study. Dr. Wheless, what were the principal findings?

Wheless: [12:09] In general, patients did well from a safety standpoint, but let me get into specifics about the study and the safety highlights. Treatment-emergent adverse events or TEAEs related to treatment occurred in 18.4% of patients. The most common was nasal discomfort, approximately 6%; headache in 2.5%; an alteration in taste, epistaxis, or somnolence in about 1.8%.

A trained observer did the nasal irritation test: 781 assessments were performed throughout the study and, in that number, 764 showed no signs of nasal irritation. A few cases of irritation were transient. There were no notable changes in olfaction.

Second point is that other than seizures, the most common treatment-emergent adverse events were nasal pharyngitis in about 12%; upper respiratory tract infection, 12% ; and pyrexia in about 10%.

Finally, we look at serious treatment-emergent adverse events. These were reported in approximately 31% of patients. However, none were considered treatment related.

There was one death due to SUDEP *[Sudden Unexpected Death in Epilepsy]* and one discontinuation due to major depression. Neither of these were considered treatment related.

Overall, patients did well from a safety standpoint. I'll remind you that the mean duration they were in this study was 17 months. Over the entire study, 82.2% of patients reported any treatment-emergent adverse event. This was irrespective of causality.

Narrator: [13:48] Dr. Wheless, how do you interpret these findings?

Wheless: [13:51] What this means to clinicians is a couple of things. One and critically important, the safety profile of diazepam nasal spray is consistent with the established safety profile of rectal diazepam.

The assessments done during this study showed no greater amounts of nasal irritation during the study than at baseline, and no clinically relevant olfactory changes. Additionally, there were no cardiorespiratory events observed.

I'll remind our listeners that in a prior study of healthy volunteers, diazepam nasal spray had comparable bioavailability and less variability compared with rectal diazepam administration.

Narrator [14:33] Now within the scope of the larger study, you and your colleagues completed several subgroup analyses based on age, use of concomitant benzodiazepines, and other factors. Please tell us what those subanalyses reveal.

Wheless [14:45] We looked at 4 subgroups that we thought would be of interest to treating clinicians and healthcare providers. The first one we looked at was the effect of age. So, we looked at children. We separated them out into patients 6 to 11 years and then our older group of 12 to 65 years. We saw that in the younger group they had slightly higher rates of treatment-emergent adverse events.91%, compared to 79% for the 12 and above group. Interestingly enough, though, they had lower rates diazepam nasal spray–related treatment-emergent adverse events. When we looked at that the younger group (6 to 11 years), there were 6.7%; the group 12 and older was 22.9%.

The second group we looked at was the group that had concomitant benzodiazepine use. We wanted to look and see if they differed in their treatment-emergent adverse events, and we showed similar rates between groups. So, in those taking concomitant benzodiazepines, this occurred in 85.6%. Those not taking them, it was 71.1%. When we looked at the treatment-emergent adverse events considered to be related to diazepam nasal spray, it was slightly higher if they had concomitant benzodiazepine use; it was 20.8%. But if they were not taking concomitant benzodiazepines, it was 10.5%.

The third subgroup we looked at was our patients that had a history of seasonal allergies or rhinitis. The bottom line was that a history of allergies or rhinitis did not appear to affect the tolerability of nasal delivery of diazepam nasal spray. We looked at their treatment-emergent adverse events. We saw they were similar between the two groups. Of those with seasonal allergies, it was approximately 86%. Without, it was approximately 80%. If we then characterize that further by diazepam nasal spray–related treatment-emergent adverse events, we again see they're similar. Those with seasonal allergies, approximately 21%. Without, 16%.

The fourth subgroup we wanted to look at was looking at was there a difference in treatment-emergent adverse events based on use of the intranasal diazepam product? So, we segregated this out by patient use, and what we saw when we looked at treatment-emergent adverse events based on monthly use of the product was that patients that used one to two doses a month reported 78%; two to five doses a month was 85%; and if they used more than five doses a month, 100% reported treatment-emergent adverse events. Again, if we segregate out those treatment adverse events as to whether they were related to the use of diazepam nasal spray, we still saw higher proportion in patients with more frequent usage. So here if it was once to twice a month, it was 11.5%; two to five doses a month was 25%; and more than five doses a month was 37.5%.

Narrator: [17:57] One aspect of the study is it enrolled a broadly generalizable epilepsy population in a community setting where concomitant benzodiazepine use was allowed, and although it did not include efficacy endpoints, an exploratory analysis of effectiveness was performed. Dr. Wheless, could you describe the results of the proxy measure used in the study for our listeners?

Wheless [18:17] Yes, one measure of effectiveness was need for the second dose in that 24-hour period. The other was just the patient's desire to keep using the product, with the thinking being that if it wasn't working, they probably would not continue in the study.

So first, let's look at the number of patients that needed a second dose. In this study, the second dose being given within that 24-hour period after initial seizure was again defined as a proxy measure for effectiveness. And in this study, 12.6% of patients required a second dose. If we look at our other measure, which was did they keep using the product, 72%, remember, continued to use it. So, we had a high long-term retention rate.

I'll remind you that in prior studies—there's a prior study based on seizure diaries—reported that slightly over half of patients would have a seizure within that 6 to 24 hours after the initial seizure in a cluster.

So the data from our study seems to suggest that this product was effective in treating seizure clusters. Effectiveness in this study was also supported by the high long-term retention rate.

Narrator: [19:37] Dr. Wheless, there's some evidence that tolerance may develop with maintenance use of benzodiazepines and other anti-seizure drugs. And tolerance is generally associated with long-term treatment or high doses. How is this concern addressed in the current study?

Wheless: [19:50] We tried to address this by looking at two markers or endpoints. The goal was to explore these two markers as a potential signal of benzodiazepine tolerance. And the two that were investigated were: 1) the use of a second dose of diazepam nasal spray within 24 hours in patients on concomitant benzodiazepines; and 2) the need for a second dose in those using diazepam nasal spray on a more frequent basis.

What did we find? The results showed no clinically relevant difference in second dose for patients with higher monthly use of diazepam nasal spray, nor for those on concomitant benzodiazepines. To highlight this, for patients using two to five doses a month, a second dose occurred in approximately 10% of their seizure clusters. For patients using concomitant benzodiazepines, 12.5% of clusters were treated within 24 hours, similar to the overall rate. So, these two exploratory markers suggest that tolerance does not appear to be a concern.

Narrator: [21:00] To sum up, what central points do you want to highlight to your colleagues about this research, Dr. Wheless?

Wheless: [21:06] There are a couple of key take-home messages I want to pass on. But before we do that, let me just remind my colleagues that this study represents one of the largest studies to date in patients with seizure clusters. The population of patients included had intractable epilepsy and seizure clusters. It was the largest number of seizure clusters recorded and doses of study drug administered, and the exposure was at least a year or more in 82% of patients.

Key points for clinicians to remember are, first, safety. Treatment-related adverse events were only reported in about 18.4% of patients and no serious treatment-emergent adverse events were considered related to treatment. Specifically, there was no respiratory depression, and there was a low overall rate of somnolence, only 6.7%.

The other bookend of safety is effectiveness. The product was effective and the results appear to apply to the broad spectrum of patients clinicians are likely to encounter. We treated children as young as six years of age. There were patients taking concomitant benzodiazepines; patients with seasonal allergies; and even patients with a prior history of status epilepticus.

The effectiveness for the product was supported by the low rate of second dose across the 24-hour period, only 12.6% of seizures, and the high retention rate of approximately 72% over a mean exposure time frame of 1.5 years. And remember, the exposure was at least a year in 82% of our patients.

Narrator: [22:49] Thank you, Dr. Wheless, for speaking with us today and sharing your expertise for this edition of the Neurelis Medical Affairs Podcast series. We very much appreciate it.

Narrator: [22:57] Before we conclude, here is some additional important safety information about Valtoco. Valtoco is contraindicated in patients with:

- Hypersensitivity to diazepam and
- Acute narrow-angle glaucoma

Benzodiazepines, including Valtoco, may produce Central Nervous System (CNS) depression. Caution patients against engaging in hazardous activities requiring mental alertness, such as operating machinery, driving a motor vehicle, or riding a bicycle, until the effects of the drug, such as drowsiness, have subsided, and as their medical condition permits.

The potential for a synergistic CNS-depressant effect when Valtoco is used with alcohol or other CNS depressants must be considered, and appropriate recommendations made to the patient and/or care partner.

Antiepileptic drugs (AEDs), including Valtoco, increase the risk of suicidal ideation and behavior. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or unusual changes in mood or behavior.

Benzodiazepines, including Valtoco, can increase intraocular pressure in patients with glaucoma. Valtoco may only be used in patients with open-angle glaucoma only if they

are receiving appropriate therapy. Valtoco is contraindicated in patients with narrow-angle glaucoma.

Valtoco is not approved for use in neonates or infants. Serious and fatal adverse reactions, including “gasping syndrome”, can occur in neonates and low-birth-weight infants treated with benzyl alcohol-preserved drugs, including Valtoco. The “gasping syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known.

The most common adverse reactions (at least 4%) were somnolence, headache, and nasal discomfort.

Diazepam, the active ingredient in Valtoco, is a Schedule IV controlled substance.

Please read full Prescribing Information, including Boxed Warning, for additional important safety information—available at www.valtoco.com.

Narrator: [25:00] To close, we would like to say thanks again, Dr. Wheless. We would also like to say thank you to our audience for joining this conversation. For more information on this particular article, please contact your Neurelis Medical Science Liaison directly or the Neurelis Medical Affairs team at medinfo@neurelis.com.

This podcast is one of a series. To access the series, as well as other resources for your patients with seizure clusters, visit NeurelisMedicalAffairs.com.