CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211635Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Original NDA
Application Number(s)	211635 (0001, 0002, 0003, 0005, 0011, 0013, 0018, 0019, 0020)
Priority or Standard	Standard
Submit Date(s)	12 DEC 2018
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PDUFA Goal Date	10 OCT 2019 (Extended to 10 JAN 2020)
Division/Office	DN2/ON/OND
Reviewer Name(s)	Natalie Getzoff, MD
Review Completion Date	09 JAN 2020
Established/Proper Name	Diazepam
(Proposed) Trade Name	Valtoco
Applicant	Neurelis
Dosage Form(s)	Single use drug-device product for nasal inhalation
Applicant Proposed Dosing Regimen(s)	5, 10, 15, or 20 mg intranasally with second dose after 4 hours if needed
Applicant Proposed Indication(s)/Population(s)	Intermittent use in adults and children six years and older with epilepsy, on stable regimens of antiepileptic drugs (AEDs), to control bouts of increased seizure activity, often referred to as cluster or acute repetitive seizures (ARS).
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients 6 years of age and older.

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Glossary

AC	advisory committee
AE	adverse event
AED	antiepileptic drug
AR	adverse reaction
ARS	acute repetitive seizures
BPCA	Best Pharmaceuticals for Children Act
BMI	body mass index
BP	blood pressure
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DNP	Division of Neurology Products
DZP NS	diazepam nasal spray
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IN	intranasal
ISE	integrated summary of effectiveness

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ISS	integrated summary of safety
ITT	intent to treat
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OXC	oxcarbazepine
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PGTC	primary generalized tonic-clonic
PGTCS	primary generalized tonic-clonic seizure
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
POS	partial onset seizures
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SJS	Stevens Johnson Syndrome
SUDEP	sudden unexplained death in epilepsy
TEAE	treatment emergent adverse event
VPA	valproic acid, valproate

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1. Executive Summary

1.1. Product Introduction

The applicant is planning to market diazepam nasal spray (DZP NS, proposed proprietary name Valtoco) in the United States (US). Valtoco is an intranasal (IN) combination drug-device product intended for the acute treatment of intermittent episodes of increased seizure activity (seizure clusters, acute repetitive seizures) in patients 6 years of age and older with epilepsy.

Diazepam (DZP), the active ingredient, is a benzodiazepine, initially approved in the United States (US) for management of anxiety in 1963 under the trade name Valium (NDA 013263). It is currently marketed as a generic drug in the US in intravenous (IV), intramuscular (IM), and oral formulations for adults and children for treatment of anxiety, symptomatic treatment of acute alcohol withdrawal, relief of skeletal muscle spasm, and as adjunctive treatment of seizures. Diazepam rectal gel (proprietary name Diastat), the listed drug (LD), is approved for management of increased seizure activity (i.e., acute repetitive seizures) in patients with epilepsy.

This application is a 505(b)(2) application and includes a new dosage form, new combination product, and new route of administration (IN). The applicant proposes treatment with 5, 7.5, or 10 mg single-use vials, administered as one IN spray (5 or 10 mg dose) or 2 nasal sprays (15 or 20 mg dose), with the allowance of a repeat dose after 4-12 hours if needed. The product is intended to be utilized on a chronic, intermittent basis, as it will likely be given as needed for each seizure cluster or episode of acute repetitive seizures. The delivery device is packaged as a single-use vial with aspirator and includes 2 or 4 vials (depending on dose).

1.2. Conclusions on the Substantial Evidence of Effectiveness

DZP NS is a new formulation of an already approved drug, and the submission is a 505(b)(2) using Diastat (diazepam rectal gel) as the LD. Efficacy was not assessed in the development program for DZP NS, and the applicant is seeking an indication consistent with that of the LD. The clinical efficacy of diazepam for the proposed indication is based on the LD as outlined in NDA-020648 and the determination of comparable bioavailability of DZP NS to Diastat.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

As this application does not include efficacy data, the determination of benefit and risk depends significantly on the efficacy data from the LD. The overall benefit-risk analysis of

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Valtoco (diazepam nasal spray) is therapeutically acceptable. The LD, Diazepam rectal gel, has been marketed in the United States for intermittent use to control bouts of increased seizure activity since 1997 and has a well characterized safety profile. According to the Clinical Pharmacology reviewer for this application, Valtoco has been shown to have comparative bioavailability when compared to diazepam rectal gel. No new or unexpected adverse events were discovered in the course of the development program of Valtoco in healthy adults and patients with epilepsy 6 years of age and older. There are no clinical safety issues impeding the approval of the proposed product.

1.4. Patient Experience Data

As described below, this application is based on bioavailability studies and one open-label long-term safety study. No efficacy data are included. Therefore, patient experience data are not relevant to this application.

2. Therapeutic Context

2.1. Analysis of Condition

The proposed indication for Valtoco (diazepam nasal spray, DZP NS) is for treatment of intermittent episodes of increased seizure activity, (b) (4) seizure clusters and acute repetitive seizures, in patients 6 years and older. Seizure clusters and acute repetitive seizures are used synonymously, and although not clearly defined as a condition by the International League Against Epilepsy, there have been several different proposed clinical and research definitions in the published literature. For research and labeling purposes, the Agency has consistently used the same definition that was previously utilized for the clinical trials of rectal diazepam in the treatment of acute repetitive seizures. Seizure cluster is "an episode of multiple complex partial or generalized (tonic, clonic, tonic clonic, atypical absence, or myoclonic) seizures occurring within a 24-hour period in adults (12-hour period in children), with a pattern distinguishable from the patients' usual seizure pattern, and with onset readily recognizable by a caregiver, such as a parent."[1,2]

Although exact prevalence is unknown, the prevalence of seizure clusters was recently estimated to be approximately 2.5/10,000 in a recent UK study[3]. The most significant risk factor

[1] Peripheral and Central Nervous System Drugs Advisory Committee Meeting #45; November 15, 1996
[2] Cereghino JJ, Mitchell WG, Murphy J, et al. Treating repetitive seizures with a rectal diazepam formulation. Neurology 1998; 51:1274-1282
[3] Martinez, C, Sullivan T, Hauser WA. Prevalence of acute repetitive seizures (ARS) in the United Kingdom. Epilepsy Res 2009; 87:137-143.

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for incurring seizure clusters is having intractable epilepsy or having a history of prior seizure clusters. Seizure clusters are primarily found in a subset of patients with epilepsy and describe seizures of any type that occur in a group or cluster over a number of hours/days. Seizure clusters often result in emergency room visits with or without hospitalization, have negative impact on productivity, and disrupt daily life, including school and work, for both patients and their caregivers.[4] Although seizure clusters may resolve spontaneously, they often progress to prolonged seizures or status epilepticus[5]. Status epilepticus is a potentially life-threatening complication of seizure clusters, and early treatment is considered imperative to prevent such progression.[6]

Thus, the goals of treatment of seizure clusters are seizure cessation and prevention of further seizures. Acute benzodiazepine treatment is considered the standard for effective and rapid seizure termination[4], and two drugs, Nayzilam and Diastat, are approved for that use (see Section 2.2 below). Available routes of administration for benzodiazepines include oral, buccal, sublingual, nasal, intramuscular, intravenous, and rectal. The widely available and approved parenteral formulations of lorazepam and diazepam are only able to be administered by EMS or ER personnel. These drugs require IV placement and transportation, often resulting in significant treatment delays. There are concerns regarding slower absorption and risk of aspiration when using the oral route for acute seizure treatment.[4]

2.2. Analysis of Current Treatment Options

Two drugs (including the LD) are approved by the US Food and Drug Administration (FDA) for acute repetitive seizures: diazepam rectal gel (Diastat) and IN midazolam (Nayzilam).

Diazepam rectal gel, the listed drug (NDA-020648), was approved in the US for use by caretakers for this situation in 1997. However, it is often not practical to administer or may not be socially accepted by the patient or caregiver, especially for adolescent and adult patients, leading some patients to forgo treatment and hope the seizure cluster will resolve, rather than utilize rectal diazepam[7,8].

The approval of Diastat was based on two clinical trials. Study 1 was a randomized, placebo-controlled sequential dose trial comparing diazepam rectal gel to placebo in seizure frequency after dosing for a seizure cluster. A total of 91 children (2 years and older) and adults were enrolled in this trial, and all patients received 2 doses of the drug or placebo. Adults were

[4] Haut, SR. Seizure Clusters: characteristics and Treatment. Curr Opin Neurol. 2015; 28(2):143-50.
[5] Mitchell WG. Status epilepticus and acute serial seizures in children. J Child Neurol 2002; 17(Suppl 1):S36-S43.
[6] Cereghino, JJ. Identification and Treatment in Acute Repetitive Seizures in Children and Adults. Curr Treat Options Neurol (2007), 9: 249-255.
[7] Tatum WO. Adult patient perceptions of emergency rectal medications for refractory seizures. Epilepsy & Behavior 3 (2002) 535–538
[8] Wilson MT, Macleod S, O'Regan M. Nasal/buccal midazolam use in the community. Arch Dis Child 2004;89:50–51

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observed for 24 hours and children were observed for 12 hours. The median seizure frequency for the diazepam rectal gel treated group was 0.0 seizures per hour, compared to a median seizure frequency of 0.3 seizures per hour for the placebo group, a difference that was statistically significant (p <0.0001). Study 2 was a placebo-controlled, randomized, double-blind study comparing single doses of diazepam rectal gel and placebo in 53 children and 61 adults. The dose was given at the onset of the identified episode and patients were observed for a total of 12 hours. The primary outcome in this study was seizure frequency. The median seizure frequency for the diazepam rectal gel-treated group was 0.0 seizures per 12 hours, compared to a median seizure frequency of 2.0 seizures per 12 hours for the placebo group, statistically significant at p <0.03.[9]

Nayzilam, an IN formulation of midazolam, has recently been approved under NDA-211321 for a very similar indication as proposed by the applicant for DZP NS. This approval was primarily based on a single, randomized, double-blind, placebo-controlled efficacy and safety study of IN midazolam in patients who were ≥12 years of age with epilepsy and confirmed diagnosis of seizure clusters. The primary endpoint of that trial was the comparison of IN midazolam to IN placebo arms in the proportion of subjects with treatment success (seizure termination within 10 minutes AND no recurrence within 6 hours). The difference between groups was 19.4%, statistically significantly favoring IN midazolam (1-sided p=0.0069).[10]

Non-rectal, non-IV routes of administration may be administered more rapidly than rectal or IV routes; therefore, off-label treatment options for ARS frequently include buccal lorazepam, diazepam, and midazolam.

[9] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020648s014lbl.pdf
[10] NDA-211321, Clinical Review, Dr. Emily Freilich, page 49.

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Table 1: Summary of drugs currently approved for treatment of acute repetitive seizures

Product (s) Name	Relevant Indication	Year of Approval for ARS Indication	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Diastat (diazepam rectal gel) **Listed Drug**	Management of selected, refractory, patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure activity	1997	Intranasal, 2nd dose may be given 4-12 hours after initial dose, if needed. Weight- and age-based dosing categories; 5, 7.5, 10, 12.5, 15, 17.5, and 20 mg.	Study 1: primary efficacy based on reduction of seizure frequency during the period of observation and a global assessment that assessed severity, nature, and frequency of the seizures. Median seizure frequency for Diastat group was 0 seizures/hour, compared to 0.3 seizures/hour in the placebo group ($p< 0.0001$). Time to next seizure prolonged in Diastat group compared to placebo ($p=0.0002$). Study 2: Comparison of single dose of Diastat and placebo in treatment of a single seizure cluster episode (12 hours). Primary outcome: seizure frequency in Diastat pts was 0 per hour and 2 per hour in pts on placebo ($p=0.0072$); 55% and 34% of Diastat and placebo treated patients, respectively, were seizure free during the observation period.	Most frequent AE during the rectal diazepam trials was somnolence; less frequent AEs: diarrhea, ataxia, dizziness, and euphoria. Warnings in the diazepam label: Concomitant use w/opioids: profound sedation, respiratory depression, coma, and death

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Product (s) Name	Relevant Indication	Year of Approval for ARS Indication	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Nayzilam (midazolam) nasal spray	Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older	2019	Intranasal, single 5 mg dose, may be repeated after 10 min if no response	Nayzilam was studied for the outpatient treatment of a single seizure cluster in 292 patients. Statistically significant increase in number of patients taking Nayzilam achieving treatment success (defined as "termination of seizures within 10 minutes after the initial blinded dose of study drug and the absence of a recurrence of seizures within 6 hours of the initial blinded dose of study drug") than seen in placebo (53.7% and 34.3%, p=0.011)	Somnolence most notable AE in the Nayzilam trial. Warnings for midazolam: CNS Depression from concomitant use with other CNS depressants or moderate or strong CYP3A4 inhibitors: prolonged sedation; Suicidal Behavior and Ideation (class warning); Impaired cognitive function Contraindication: acute narrow angle glaucoma

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3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This 505(b)(2) application relies on the FDA's findings of safety and effectiveness for the LD (Diastat, diazepam rectal gel). Primary safety data for Valtoco were mainly generated from two open label studies (Studies 001.04 and 001.05) described in section 8 of this review.

Diazepam was approved as an oral tablet by the US FDA on November 15, 1963 for the management of anxiety disorders. Other approved indications include symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis in the setting of acute alcohol withdrawal; relief of skeletal muscle spasm due to reflex spasm, spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia), athetosis, and stiff-man syndrome; and adjunctively in convulsive disorders. An intravenous formulation of diazepam was approved in 1966 but is no longer marketed under the trade name. Injectable diazepam is currently marketed in the US under several ANDAs.

Diastat was approved in 1997 for *"management of selected, refractory, patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure activity".* See Section 2.2 for summary of the clinical trial data for Diastat.

3.2. Summary of Presubmission/Submission Regulatory Activity

See below for timeline of key regulatory activity since IND-112621 was opened in 2011:

- PIND meeting minutes (12/2/2011): discussed using Diastat as the LD, simplifying the indication to acute repetitive seizures, requiring pharmacokinetics (PK) data during the ictal or peri-ictal period, verifying that IN absorption in pediatric patients is similar to that in adults, and determining bioequivalence to the LD (not IV diazepam)
- Type C Written Response Only (WRO, 10/27/2015) to (among other issues) discuss the continued need for a PK study in patients with epilepsy (ictal/peri-ictal and interictal administration), the need for at least 30 adult epilepsy patients in the PK study and 10 patients with administration during a seizure (ictal), the need for enrollment of sufficient pediatric patients in the long-term safety study, the requirement to assess local IN toxicity including evaluation of the functions of smell and taste (and including at least 10 patients with at least 3 exposures to the product), and the need for human factors testing. The sponsor-proposed plan to (b) (4) .
- Response to email dated 1/29/2016 (2/5/2016): reiterated concerns about anticipated variability in PK (absorption), nasopharyngeal anatomy, and feasibility of delivery (e.g.,

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behavioral issues with administration to children under 12 years of age), (b) (4) Sponsor was told that demonstration of comparable bioavailability between rectal and IN diazepam in the healthy adults (currently proposed Study 01.03), reasonably congruent results between ictal/peri-ictal and interictal PK in adults (adults in Study 01.04), and no notable differences between the PK in healthy adults and adult patients with epilepsy in a cross study comparison would be necessary, as well as chronic safety data (sponsor's originally proposed 50 adult and 50 pediatric patients would likely be sufficient).

- Advice/Information Request (4/14/2016) FDA pediatric ethics team determined that the administration of IN diazepam in pediatric patients during the interictal period does not offer a prospect of direct benefit and presents greater than minimal risk. However, this risk is no more than a minor increase over minimal risk and the protocol was deemed acceptable. Proposed sample size of 15 pediatric patients (6-16 years of age) in Study 001.04 was potentially too small, but its adequacy would be a matter of review. For the long-term safety study, 50 adult and 50 pediatric patients was again recommended with at least 30 patients in the 6-12-year-old group.
- PreNDA meeting (3/30/2018) to discuss the data necessary to support a 505(b)(2) NDA for DZP NS. Current level of PK and safety data were discussed, and FDA conveyed that the adequacy of the data (including pediatric) will be a matter of review. Twelve-month safety data were still needed, as well as safety data from patients who have received multiple doses.

3.3. Foreign Regulatory Actions and Marketing History

Diazepam for IN administration for the treatment of seizures is not currently marketed in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable to this review.

4.2. Product Quality

See the OPQ review for a complete discussion of drug product and manufacturing deficiencies.

There are two known diazepam related impurities: USP Related Compound A (RCA) and USP Related Compound B (RCB). The proposed acceptance criteria for RCA and RCB exceed the ICH qualification threshold, no more than 0.5%, for the maximum daily dose of diazepam (40 mg)

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and have not been adequately qualified. Specifically, assessment of stability identified an increase in (b) (4) total impurities with significant increases in RCB: (b) (4)% observed after accelerated storage for 6 months and (b) (4)% after long-term storage for 18 months. As noted by OPQ, these exceed the 0.5% ICH qualification threshold for one batch of the 5 mg strength and reach the 0.5% threshold at 9 months for two of the three 10 mg batches. Reduction of the RCB to the 0.5% ICH threshold results (b) (4) is not a commercially viable shelf life, (b) (4)

Additionally, OPQ identified several manufacturing deficiencies, which are discussed in their review. The initial OPQ recommendation was for a complete response based on these product and manufacturing deficiencies. However, the applicant submitted a major amendment on 26 SEP 2019, which provided sufficient information to support their proposed commercial distribution.

4.3. Clinical Microbiology

Not applicable to this review.

4.4. Nonclinical Pharmacology/Toxicology

To evaluate the safety of DZP NS, the sponsor conducted 3 GLP IN toxicity studies of the clinical formulation (NRL-1): Two 4-week studies (in rat and dog) and a 6-month study in rat. These studies did not indicate any unexpected toxicity at doses and dosing frequencies greater than those proposed in humans. Dr. Fisher noted that toxicity studies in juvenile animals were not conducted; therefore, there are no nonclinical data to support safety in pediatric patients. However, there are sufficient clinical safety data in pediatric patients down to age 6 years to support approval.

There are two degradants of DZP NS that meet or exceed the ICH qualification threshold of 0.5% for a drug product having a maximum daily dose of 40 mg. The sponsor set specification limits of (b) (4)% for substance A and (b) (4)% for Substance B. From Dr. Fisher's review: *"To qualify related substances A and B, (Q)SAR analyses of each degradant were conducted by the sponsor. These and the FDA (Q)SAR evaluations predicted that both degradants were negative for mutagenicity. However, for a chronic intermittent indication, a 3-month toxicity study in one species would generally be needed to qualify an impurity unless adequate toxicology data were available in the scientific literature (ICH Q3B(R2)). The sponsor's toxicology assessment of the impurities stated that no toxicological data were found in the available literature for diazepam related compounds A and B,* (b) (4) *Because levels of the degradants were low (<* (b) (4) *%) in the drug batches used in the pivotal toxicity studies, the information provided is inadequate to qualify the impurities at the proposed specification limits.*

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Therefore, the specification limit for each impurity needs to be lowered to the qualification threshold." If the specification level is lowered to 0.5%, the expiry would be (b) (4) months.

The nonclinical recommendation is for approval, provided that the specification limits for Substances A and B are lowered to 0.5%.

4.5. Clinical Pharmacology

Please see the Office of Clinical Pharmacology (OCP) review for a full discussion of the pharmacokinetics data.

The applicant provided clinical pharmacology information from three studies in healthy volunteers and one study in patients with epilepsy. PK bridging between Valtoco and the LD was established in Study 03.

1. DIAZ.001.01 (Study 01): comparison of an earlier formulation of DZP NS to IV diazepam
2. DIAZ.001.03 (Study 03): comparison of DZP NS to diazepam rectal gel (LD)
3. DIAZ.001.02 (Study 02): a dose proportionality study of DZP NS (5 mg, 10 mg and 20 mg) and two doses (10 mg, 4 hours apart) of DZP NS
4. DIAZ.001.04 (Study 04): a PK study in patients with epilepsy under ictal/peri-ictal and interictal conditions

Overall, the absolute bioavailability was ~97% for DZP NS. In an ascending dose PK study in healthy adults (Study 01), the T_{max} following nasal administration of DZP NS was ~1.5 hours. The mean elimination half-life of diazepam after administration of a 10 mg dose of DZP NS was ~49 hours. The PK parameters of diazepam and nordiazepam following diazepam nasal spray administration were found to be essentially proportional.

Study 03 was the "pivotal relative BA study" upon which PK bridging to the LD was determined. As per the OCP review, the geometric mean ratio (GMR) for Cmax in the 15 mg group was 85% [90%CI: 57%, 126%]. The GMR for AUC0-∞ was 74% [53%, 102%]. For 20 mg group, the GMR for Cmax was 118% [69%, 202%], and the GMR for AUC0-∞ was 100% [65%, 152%]. OCP deemed that some of these differences were due to the greater impact of weight/BMI on the exposure of diazepam rectal gel, especially at the 15 mg dose. Although the results were outside the range of the usually accepted determination of bioequivalence, the comparison of DZP NS to DZP rectal gel showed that diazepam PK parameters were less variable for the nasal spray formulation (2 to 4-fold lower variability) as compared to the LD and within the range of those seen with diazepam rectal gel.

Because the conditions of use in the ictal/peri-ictal period could potentially impact nasal administration and thus the PK, PK was assessed during peri-ictal/ictal and interictal states in patients with epilepsy in Study 04. The mean PK profiles appeared similar with a large overlap following IN administration of DZP NS in patients during ictal/peri-ictal or interictal states. A cross study comparison between patients with epilepsy and healthy volunteers was also

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performed, which revealed lower levels of diazepam in patients with epilepsy compared to healthy volunteers (AUC lower ~ 25% to 33% and Cmax ~34% to 42%). OCP theorizes that concomitant inducer medications may play a role in this difference.

Dosing of DZP NS is 5-20 mg, administered intranasally. The 5 mg and 10 mg doses are administered as a single spray intranasally into one nostril. The 15 mg and 20 mg doses require two nasal spray devices (7.5 mg and 10 mg, respectively), with one spray into each nostril. Dosing of DZP NS is based on weight, as summarized in Table 2 below. There are fewer dose groups with DZP NS dosing (4) than with diazepam rectal gel (7), because of lower variability in PK of diazepam when administered intranasally as compared to rectally.

Table 2: Proposed weight-based dosing categories

6 - 11 years (0.3mg/kg)		≥12 years (0.2mg/kg)	
Weight (kg)	**Dose (mg)**	**Weight (kg)**	**Dose (mg)**
10 - 18	5	14 - 27	5
19 - 37	10	28 - 50	10
38 - 55	15	51 - 75	15
56 - 74	20	76 and up	20

4.6. Devices and Companion Diagnostic Issues

The CDRH review has not been completed at the time of this review.

4.7. Consumer Study Reviews

Please see the Division of Medication Error Prevention and Analysis (DMEPA) review for a full discussion of the results of the human factors study.

The DMEPA review identified some errors/failures during the Human Factors study that may lead to underdosage or overdosage of the product. However, the clinical risk associated with these underdosage or overdosage scenarios is mild, because of the wide acceptable dose ranges by weight for diazepam.

5. Sources of Clinical Data and Review Strategy

Two open-label studies of DZP NS form the primary basis of this review (see Table 3):

- Study 04: Open-label PK, safety, and tolerability study of DZP NS during ictal/ peri-ictal and interictal periods in pediatric and adult patients with epilepsy and seizure clusters
- Study 05: Open-label, chronic safety study in pediatric and adult patients with epilepsy and seizure clusters.

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5.1. Table of Clinical Studies

Table 3: Clinical Studies in Patients Contributing Safety Data

Study ID	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. enrolled/ completed	Study Population	No. of Centers
DIAZ 001.04	Phase 1, open-label, PK and safety study in patients with epilepsy under ictal/peri-ictal and interictal conditions	2 IN diazepam doses (weight-based) administered during 1) the ictal or peri-ictal period and 2) again under non-seizing (interictal) conditions separated by a minimum 14-day washout period	Primary: comparison of PK of IN diazepam during ictal/peri-ictal and interictal periods in adult and pediatric patients. Safety evaluated using descriptive statistics: adverse events (AEs), clinical laboratory evaluations, vital sign (VS) measurements, ECGs, and physical examination findings	Up to 65 days	57 (ongoing)	Patients with epilepsy who might need benzodiazepine for control of seizure	19 (US)
DIAZ 001.05	Phase 3, repeat dose, open-label, safety study in Epilepsy subjects	IN administration (weight-based dosing) as needed for ARS separated by 4-12 hrs	Safety evaluated using descriptive statistics: AEs, clinical laboratory evaluations, VS, ECGs, and physical examination findings	12-months	153 (ongoing)	Epilepsy patients with frequent breakthrough seizures or ARS	24 (US)
Healthy Volunteer Studies							
DIAZ 001.01	Phase 1, open-label, randomized, 3-treatment, 3-period, 6-sequence crossover bioavailability study	Diazepam NS suspension (NRL-1.A) single 10-mg intranasal dose Diazepam NS solution (NRL-1.B) single 10-mg intranasal dose	Primary: comparison of PK of the diazepam formulations in healthy adult volunteers Safety evaluated using descriptive statistics: AEs, laboratory evaluations, VS,	3 single doses administered over 9 weeks	24	Healthy volunteers	1 (US)

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Study ID	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. enrolled/ completed	Study Population	No. of Centers
		Diazepam IV, 5 mg/mL, over 1 minute	ECGs, and physical examination findings				
DIAZ 001.02	Phase 1, open-label, randomized, 3 single dose, 3-period, 6-sequence crossover study, followed by a fourth 2-dose period	3 IN single doses (5, 10, 20 mg) separated by a minimum 28-day washout period followed by a 4th IN 2-dose treatment separated by 4 hrs	Primary: comparison of PK of the 3 IN diazepam doses in healthy adult volunteers Safety evaluated using descriptive statistics: AEs, laboratory evaluations, VS, ECGs, and physical examination findings	21 weeks	36 enrolled 29 completed	Healthy volunteers	1 (US)
DIAZ.001.03	Phase 1, open-label, randomized, controlled, single-dose, 3-treatment, 3-period, 6-sequence crossover study	3 single weight-based doses of diazepam (IN, rectal, and oral) separated by a minimum 28-day washout period	Primary: comparison of PK of diazepam (IN, PR, and PO) in healthy adult volunteers Safety evaluated using descriptive statistics: AEs, laboratory evaluations, VS, ECG results, and physical examination findings		48 enrolled, 46 rec'd IN diazepam 44 completed	Healthy volunteers	1 (US)

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5.2. Review Strategy

A safety determination was made by evaluating data from one open-label PK and safety study (Study 001.04) and one open-label chronic safety study (Study 001.05) in adult and pediatric patients with epilepsy. This review focuses solely on safety. No efficacy data were included in the submission, and efficacy will be determined based on comparative bioavailability. A PK analysis for exposure and dosing was performed by the Office of Clinical Pharmacology and is summarized in their review.

6. Review of Relevant Individual Trials Used to Support Efficacy

Not applicable. See Section 8.2 for a description of the studies used to support safety for chronic intermittent use in patients 6 years of age and older to control cluster or acute repetitive seizures.

7. Integrated Review of Effectiveness

Efficacy is based on comparative bioavailability of DZP NS to the LD (diazepam rectal gel).

8. Review of Safety

8.1. Safety Review Approach

The primary safety data were primarily generated from one open-label PK and safety study and from one uncontrolled, open-label, chronic safety study in adult and pediatric patients with epilepsy who used DZP NS as needed to treat bouts of increased seizures over at least 6 months.

- Study 04: Multicenter, open label, PK and safety study of DZP NS in adults and pediatric patients (ages 6-16 years) during ictal/peri-ictal and interictal periods.
- Study 05: Multicenter, open-label, single-arm chronic safety study of DZP NS in adults and pediatric patients (ages 6-16 years) with bouts of uncontrolled seizures (seizure clusters or ARS).

Three phase 1 studies in healthy volunteers provided contributory safety data.

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Most of my independent safety analyses were performed on pooled datasets from Studies 04 and 05.

A 120-day Safety Update was submitted on 8 APR 2019 and was reviewed. Ten more patients were enrolled in Study 05 after the original data cutoff and were included in the 120-day Safety Update. The safety analyses were performed primarily on the data included in the original NDA submission. Review of the 120-day Safety Update did not materially change overall TEAE rates and did not raise any new clinical concerns.

The safety analysis focused on treatment-emergent adverse events (TEAEs), SAEs, severe TEAEs, most common TEAEs, and TEAEs that led to discontinuation. An analysis was performed on TEAE incidence in specific age subgroups (6 to <12, 12 to <18, and ≥18 years).

Some AEs were coded under slightly different terms, although the underlying events were very similar and/or related. Therefore, several AE terms were recoded to avoid underestimating prevalence of a specific adverse event. Some terms were also recoded for ease of review, although none rose to the level of a new safety concern. Table 4 shows the original AE code on the left and revised codes on the right. Additionally, some related TEAE preferred terms were grouped together but not recoded, such as nausea/vomiting, ataxia/gait disturbance/ balance disorder, and somnolence/sedation/fatigue/lethargy.

Table 4: Recoded AE Codes to Group Similar Terms

Original Coded Preferred Term(s)	Recoded Term
Petit mal seizures, Epilepsy, Seizure Cluster, Loss of Consciousness	Seizure
Major Depression	Depression
Migraine	Headache
Rhinalgia	Nasal Discomfort
Viral upper respiratory tract infection	Upper Respiratory Tract Infection
Viral gastroenteritis	Gastroenteritis

Of note, there were no placebo-controlled data for review; therefore, any conclusions regarding the clinical meaningfulness of observed adverse events may not be definitive.

8.2. Description of Clinical Trials Used to Support Safety

8.2.1. Study DIAZ.001.04 (Study 04):

Study 04 is an ongoing multi-center, open-label, single arm, Phase 1 study to investigate the PK and safety of IN diazepam in patients 6 years of age and older with epilepsy. The primary purpose of the study was to compare the PK of IN diazepam during ictal/peri-ictal and interictal conditions. The planned sample size was initially to be 45 patients; however, 57 patients were enrolled by the cutoff date (30 APR 2018), and safety data was available for 50 patients. Enrollment of primarily pediatric patients was ongoing at the time of the NDA submission.

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Patients were enrolled in the study for up to 65 days. Doses were based on weight categories (see Section 4.5) and the same dose was to be administered to patients in the ictal/peri-ictal and interictal periods. In most patients, ictal/peri-ictal dosing occurred first in an epilepsy monitoring unit or at a clinical study site, followed by interictal dosing at a clinical site after a 28-day washout period.

Blood samples for PK assessments were collected at baseline, and at 15, 30, and 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, and 6 hours after dosing. Safety was assessed via treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs), clinical laboratory monitoring, vital signs, ECGs, and physical and neurological examinations. Local toxicity to the nasopharynx was prospectively evaluated. Smell tests (NIH Toolbox Odor Identification Test) were administered at baseline, at 1 and 4 hours post dosing, and at discharge. Nasal irritation (mucosal erythema, mucosal edema, nasal discharge, mucosal crusting and mucosal epistaxis) was assessed on separate scales prior to each dose of DZP NS (baseline); at 30 minutes; at 1, 2, 4, and 6 hours post dose; and at discharge.

8.2.2. Study DIAZ.001.05 (Study 05):

Study 05 is an ongoing multi-center, open-label, single arm, Phase 3 chronic safety study of IN diazepam in patients 6 years of age and older. The primary purpose of the study was to evaluate the long-term safety of IN diazepam in adult and pediatric patients (≥6 years of age) when used on a chronic, intermittent basis to treat ARS. A total of 122 patients were enrolled and received at least one dose of DZP NS by the cutoff date (31 OCT 2018). Enrollment of primarily pediatric patients was ongoing at the time of NDA submission. Patients were to be enrolled in the study for up to 1 year. Doses were based on weight categories (see Section 4.5).

Safety was assessed via treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs), clinical laboratory monitoring, vital signs, ECGs, nasal toxicity, and physical and neurological examinations. Smell tests was conducted at baseline and at each study visit. The NIH Toolbox for Odor Identification Test was used for smell tests. Nasal examination and irritation assessments (nasal irritation, mucosal erythema, mucosal edema, nasal discharge, mucosal crusting, and mucosal epistaxis) were performed at baseline and at each study visit.

8.3. Review of the Safety Database

8.3.1. Overall Exposure

During the development program (and prior to the cutoff of 31 OCT 2018), 272 unique subjects were exposed to DZP NS, as summarized in Table 5 below.

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Table 5: Cumulative Exposure to DZP NS in all studies

Study	DZP NS (mg)				Unique Subjects
	5	10	15	20	
DIAZ.001.01	-	24	-	-	24
DIAZ.001.02	36	36	-	36	36
DIAZ.001.03	-	-	18	28	46
DIAZ.001.04	-	13	19	25	57
DIAZ.001.05	3	31	38	50	109*
DIAZ.001.04 and 001.05 (pooled primary safety dataset)	***3***	***38***	***52***	***72***	***164****
Total	39	104	75	139	272

*13 patients transitioned from Study 04 to Study 05; therefore, they are not counted as unique subjects in this assessment.
**One patient received 10 mg during Study 04 and 20 mg during Study 05, hence the discrepancy between the number of patients per dose group and the total number of patients in the pooled dataset for Studies 04 and 05.
Source: ISS, verified

All clinical safety data were generated in Studies 04 and 05 and, for the purpose of this review, have been combined into a single dataset ("primary safety dataset"). The data from these studies constitute the safety database and provide the primary basis for comparisons of frequencies of adverse events, abnormal laboratory values, electrocardiograms, nasal toxicity, and vital signs. The primary safety database, for the purpose of this NDA review, includes a total of 164 patients who were exposed to at least one dose of DZP NS in Studies 04 and 05 prior to the cutoff dates for each study (Table 6) and not including the patients described in the 120-day safety update.

Table 6: Total Exposure (primary safety dataset)

Study	Number of patients exposed to the study drug:		
	≥1 dose	≥6 months	≥12 months
Total	164	104	53
Study 04	57	0	0
Study 05	109	104	53

Source: ADSL (Studies 04 and 05)

As this product is intended to be used in a chronic, intermittent fashion, sufficient exposure based on number of doses over at least 6 months was also considered. During discussions prior to the start of Studies 04 and 05, the Division strongly recommended to the applicant that the safety database include at least 100 adult and 50 pediatric patients with at least 3 doses over at least 6 months duration. As seen in Table 7 below, 102 patients were administered at least 3 doses during Studies 04 or 05, 91 of whom were "exposed" to DZP NS over at least 6 months. Because of the intermittent nature of acute repetitive seizures, the duration of exposure was considered to start when the drug was initially given to the patient (usually when consent was signed), not from the date of the first administration.

Table 7: Exposure of patients with ≥3 doses of DZP NS (primary safety dataset)

	DZP NS 5 mg (N=2) n (%)	DZP NS 10 mg (N=23) n (%)	DZP NS 15 mg (N=32) n (%)	DZP NS 20 mg (N=48) n (%)	Total (N=102) n (%)
Duration of Exposure					
<6 months	0 (0.0)	6 (26.1)	3 (21.9)	2 (4.2)	11 (10.8)
6 to <12 months	1 (50.0)	7 (30.4)	13 (40.6)	19 (39.6)	40 (39.2)
≥12 months	1 (50.0)	10 (43.5)	16 (50.0)	24 (50.0)	51 (50.0)
Number of Doses					
3-10 doses	1 (50.0)	10 (43.5)	12 (37.5)	19 (39.6)	42 (41.2)
11-20 doses	1 (50.0)	6 (26.1)	9 (28.1)	8 (16.7)	24 (23.5)
21-40 doses	0 (0.0)	4 (17.4)	10 (31.2)	14 (29.2)	28 (27.4)
>40 doses	0 (0.0)	3 (13.0)	1 (3.1)	4 (8.3)	8 (7.8)
Frequent User					
≥2 doses a month on average	1 (50.0)	20 (87.0)	23 (71.9)	32 (66.7)	76 (74.5)

Source: communication from applicant June 22, 2019

When the cumulative exposure data from the 120-day Safety Update was analyzed (Table 8 below), 103 patients had taken at least 3 doses of DZP NS over at least 6 months duration. Forty-six patients had used more than 20 doses during the time they participated in the studies, and 51 patients averaged at least 2 doses/month.

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Table 8: Exposure of patients with ≥3 doses of DZP NS (pooled Studies 04 and 05, incl 120-Day Safety Update)

	DZP NS 5 mg (N=3) n (%)			DZP NS 10 mg (N=29) n (%)			DZP NS 15 mg (N=35) n (%)			DZP NS 20 mg (N=46) n (%)			Total DZP NS (N=113) n (%)		
Age	**6 to <12 yrs**	**12 to <18 yrs**	**≥18 yrs**	**6 to <12 yrs**	**12 to <18 yrs**	**≥18 yrs**	**6 to <12 yrs**	**12 to <18 yrs**	**≥18 yrs**	**6 to <12 yrs**	**12 to <18 yrs**	**≥18 yrs**	**6 to <12 yrs**	**12 to <18 yrs**	**≥18 yrs**
Duration of Exposure															
<6 months	1 (33.3)	0	0	3 (10.3)	1 (3.4)	1 (3.4)	0	1 (2.9)	1 (2.9)	0	1 (2.2)	1 (2.2)	4 (3.5)	3 (2.7)	3 (2.7)
6 to <12 months	0	0	1 (33.3)	8 (27.6)	1 (3.4)	1 (3.4)	1 (2.9)	4 (11.4)	8 (22.9)	0	2 (4.3)	10 (21.7)	9 (2.0)	7 (6.2)	20 (17.7)
≥12 months	1 (33.3)	0	0	6 (20.7)	6 (20.7)	2 (6.9)	1 (2.9)	1 (2.9)	18 (51.4)	0	1 (2.2)	31 (67.4)	8 (7.1)	8 (7.1)	51 (45.1)
Number of Doses															
3-10 doses	1 (33.3)	0	1 (33.3)	8 (27.6)	1 (3.4)	2 (6.9)	1 (2.9)	2 (5.7)	10 (28.6)	0	3 (6.5)	14 (30.4)	10 (8.8)	6 (5.3)	27 (23.9)
11-20 doses	0	0	0	6 (20.7)	2 (6.9)	1 (3.4)	0	2 (5.7)	6 (17.1)	0	0	7 (15.2)	6 (5.3)	4 (3.5)	14 (12.4)
21-40 doses	1 (33.3)	0	0	2 (6.9)	2 (6.9)	0	1 (2.9)	1 (2.9)	9 (25.7)	0	1 (2.2)	16 (34.8)	4 (3.5)	4 (3.5)	25 (22.1)
>40 doses	0	0	0	1 (3.4)	3 (10.3)	1 (3.4)	0	1 (2.9)	2 (5.7)	0	0	5 (10.9)	1 (0.9)	4 (3.5)	8 (7.1)
Frequent User															
≥2 avg doses/ month	2 (66.7)	0	0	11 (37.9)	7 (24.1)	3 (10.3)	1 (2.9)	5 (14.3)	18 (51.4)	0	3 (6.5)	30 (65.2)	14 (12.4)	15 (13.3)	51 (45.1)

Source: email communication from applicant, 1/7/2020

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A total of 13 patients rolled over from Study 04 to Study 05; however, of these 13 patients, only 8 were included in the safety datasets of Studies 04 and 05 submitted to NDA-211635, because of the differences in cutoff dates between the studies (30 APR 2018 and 31 OCT 2018, respectively). These patients are summarized in Table 9 below. All but one of these patients received the same dose of DZP NS during Studies 04 and 05. Subj (b) (6) and Subj (b) (6) are the same individual. During Study 04, this patient was administered DZP NS 10 mg, and during Study 05, he received 20 mg. Therefore, the total number of patients/dose group (n=165) differ by one from the overall total of patients who were exposed to at least one dose of DZP NS during Studies 04 and 05 (n=164).

Table 9: Duration of exposure in patients who transitioned from Study 04 to Study 05 (primary safety dataset)

Study 04 Subj#	Study 05 Subj#	Study 04 Duration (days)	Study 05 Duration (days)	Time b/w 04 and 05 (days)	Overlap b/w 04 and 05 (days)	Total Duration (days)	Dose group
(b) (6)		23	356	0	1	378	15 mg
		61	256	0	1	316	20 mg
		36	453	0	15	474	20 mg
		15	388	0	1	402	15 mg
		38	193	34	0	265	10/20 mg
		30	77	43	0	150	10 mg
		128	242	0	1	369	10 mg
		47	181	0	62	166	10 mg
		31	83	0	1	113	NA
		61	81	0	1	141	NA
		41	76	0	13	104	NA
		28	60	15	0	103	NA

Highlighted cells are patients who were only included in Study 05, due to the later cutoff date for that study.
Source: communication from sponsor, dated June 22, 2019

Studies 04 and 05 are ongoing as of the time of this NDA review and continue to enroll patients (primarily pediatric patients).

Exposure in Pediatric Patients

Early in the development program, the Division conveyed to the Applicant our concerns about the potential impact of age-related differences in nasal anatomy and physiology on the pediatric population. Specifically, the nasal mucosa and geometry of the nasopharynx in younger children differ from those of adolescents and adults; therefore, the efficacy (absorption) and safety (chronic local toxicity) may differ. Feasibility of delivery may also be impacted by age (e.g., behavioral issues with administration to a child in an ictal or peri-ictal state). For these reasons, the Division conveyed to the Applicant the need for enrollment of sufficient pediatric patients in the chronic safety study (50 patients who received at least 3 doses over a duration of at least 6 months).

A total of 34 patients under 12 years of age received at least one dose of DZP NS during Studies 04 and 05, including the 120-day Safety Update. An additional 24 adolescent patients received at least one dose of DZP NS. As seen in Table 10 below, 32 pediatric patients (17 of whom were below 12 years of age) received at least 3 doses of DZP NS over a period of 6 months.

Table 10: Exposure of patients by age group, including 120-Day Safety Update

	Study 04			Study 05			Pooled		
Doses/ Duration	**6 to <12 yrs**	**12 to <18 yrs**	**≥18 yrs**	**6 to <12 yrs**	**12 to <18 yrs**	**≥18 yrs**	**6 to <12 yrs**	**12 to <18 yrs**	**≥18 yrs**
≥1 dose Valtoco	N=58			N=132			N=175		
	11 (6.3)	7 (4.0)	40 (22.9)	28 (16.0)	21 (12.0)	83 (62.9)	34 (19.4)	24 (13.7)	117 (66.9)
≥3 doses and ≥6 mos				N=100			N=103		
				16 (15.5)	14 (13.6)	70 (68.0)	17 (16.5)	15 (14.6)	71 (68.9)

Source: email communication from applicant, 1/9/2020

Reviewer's Comments: Assessment of chronic safety in pediatric patients was of interest and was discussed during several meetings with the Applicant. Because safety concerns in the youngest children were important, the Division recommended that Neurelis enroll 50 pediatric patients with at least 3 doses over 12 months, 30 of whom should be 6 to <12 years of age. During the pre-NDA meeting in March 2018, the Applicant noted that recruitment of pediatric patients was particularly challenging and that it was unlikely that the planned NDA submission would include chronic safety data in 50 pediatric patients. The Division stated that the adequacy of the safety data provided in the NDA would be a matter of review. A total of 58 pediatric patients received at least one dose of DZP during Studies 04 and 05 and including patients from the 120-day Safety Update, 34 of whom were <12 years of age.

In general, the safety of the active ingredient is well-understood in the pediatric

population, and the LD is approved for use in pediatric patients 2 years and older. In presubmission discussion with sponsors, we often recommend that sponsors enroll conservative numbers of patients into open label safety studies to assure that adverse effects in specific populations, as well as the overall study population, may be identified and characterized. In this case, since there was no significant difference in overall AEs and local nasal AEs between pediatric and adult patients, and there were 51 adult patients with ≥12 month duration exposure, we believe that the number of pediatric patients in the short-term epilepsy study and the open label chronic safety study was sufficient to characterize safety in patients 6 years and older.

Disposition

As of the interim analysis cutoff date of 24 APR 2018 for Study 04, a total of 50 patients had been enrolled with 42 (84%) having completed the study and 8 patients still ongoing. No patients discontinued participation early. In Study 05, 153 patients were enrolled (Table 10). As of the cutoff date, 31 patients (20.3%) completed the study, and 96 patients (62.7%) were ongoing. A total of 13 patients (8.5%) discontinued from the study and 11 patients (7.2%) were enrolled, but not dosed.

Table 11: Study disposition, Study 05

	DZP NS 5 mg n (%)	DZP NS 10 mg n (%)	DZP NS 15 mg n (%)	DZP NS 20 mg n (%)	Total n (%)
Enrolled	6 (100)	43 (100)	41 (100)	52 (100)	153 (100)
Enrolled and Dosed (safety pop)	3 (50.0)	31 (72.1)	38 (92.7)	50 (96.2)	122 (79.7)
Enrolled Not Dosed					11 (7.2)
Discontinued before Dosing	0	1 (2.3)	0	1 (1.9)	2 (1.3)
Completed Study	1 (16.7)	2 (4.7)	13 (31.7)	15 (28.8)	31 (20.3)
Premature Discontinuation	0	1 (2.3)	5 (12.2)	7 (13.5)	13 (8.5)
Lost to follow-up	0	0	0	1 (1.9)	1 (0.7)
Due to SAE	0	0	0	1 (1.9)	1 (0.7)
Withdrawal by subject	0	1 (2.3)	4 (9.8)	5 (9.6)	10 (6.5)
Other	0	0	1 (2.4)	0	1 (0.7)
Ongoing Participation	5 (83.3)	39 (90.7)	23 (56.1)	29 (55.8)	96 (62.7)

Source: ADSL (Studies 04 and 05)

8.3.2. Relevant characteristics of the safety population

Out of the 164 patients in the pooled safety database, 26 (15.9%) were 6-11 years of age, 22 (13.4%) were 12-17 years of age, and 116 (70.7%) were 18 years or older. About half (51%) were female. The majority of the patients were white (81.1%).

Table 12: Patient Demographics, primary safety dataset

Category	Study 04 N = 50	Study 05 N = 122	Pooled N=164
Age (years)			
Mean (SD)	30.6 (14.7)	27.3 (15.2)	28.3 (15.0)
Min, Max	6, 59	6, 65	6, 65
Age groups (years) n (%)			
6-11	7 (14)	21 (17.2)	26 (15.9)
12-17	4 (8)	18 (14.8)	22 (13.4)
Adults (≥18)	39 (78)	83 (68)	116 (70.7)
Adolescents and Adults (≥12)	43 (86)	101 (82.8)	138 (84.1)
Sex, n (%)			
Female	26 (52)	63 (51.6)	84 (51.2)
Male	24 (48)	59 (48.4)	80 (48.8)
Ethnicity, n (%)			
Not Hispanic/Latino	36 (72)	110 (90.2)	141 (86)
Hispanic/Latino	14 (28)	12 (9.8)	23 (14)
Race, n (%)			
White	39 (78)	100 (90.0)	133 (81.1)
Black	5 (10)	11 (9.0)	16 (9.8)
Asian	0	3 (2.5)	3 (1.8)
Pacific Islander	1 (2)	5 (4.1)	6 (3.7)
Other	5 (10)	3 (2.5)	6 (3.7)

Source: ADSL (Studies 04 and 05)

8.3.3. Adequacy of the safety database

Based on the characteristics in Table 3, the development program is deemed to provide generally adequate information about the safety of intermittent IN diazepam use to treat ARS in patients with epilepsy >6 years of age especially since the sponsor is relying on the LD for efficacy data. The primary limitation of the safety data included in this NDA is that there were no placebo controls for comparison; therefore, the primary assessment of safety remains dependent on data from the placebo-controlled trials of the LD.

8.4. Adequacy of Applicant's Clinical Safety Assessments

8.4.1. Issues Regarding Data Integrity and Submission Quality

No significant issues with the safety datasets were identified.

8.4.2. Categorization of Adverse Events

In the protocols of both Studies 04 and 05, adverse events (AEs) were defined as *"any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an*

investigational (medicinal) product (IP) or other protocol-imposed intervention", regardless of the relationship to the study drug. MedDRA version 19.0 was used for coding in Study 04 and version 20.1 was used for coding in Study 05.

For the purpose of the safety analysis, treatment emergent adverse event (TEAEs) were defined in both studies as *"events that were not present at baseline, or if present at baseline, worsened in severity."*

A serious adverse event was defined in the study protocols as *any untoward medical occurrence …that is characterized by one or more of the following:*

- *Results in death*
- *Is life-threatening*
- *Requires in-subject hospitalization or prolongation of existing hospitalization*
- *Results in persistent or significant disability/incapacity*
- *Is a congenital anomaly/birth defect*
- *Important medical events.*

AEs were collected from the date of informed consent for both trials and until the last follow-up visit. AEs were followed until resolution, at the discretion of the PI.

Reviewer's comment: The adverse event definitions and characterizations used in Studies 04 and 05 are acceptable.

8.4.3. Routine Clinical Tests

In Study 04, clinical laboratory data were collected at screening and baseline. A serum pregnancy test was performed on women of child-bearing age at screening, and a urine pregnancy test was performed at baseline.

In Study 05, clinical lab data were collected at screening and on days 150, 270, and 365. A serum pregnancy test was performed on women of child-bearing age at screening, and urine pregnancy tests were performed on days 30, 90, 150, 210, 270, 330, and 365.

Clinical laboratory tests in both studies consisted of

- Hematology: Hemoglobin, Hematocrit, RBC, Platelet count, WBC and differential, Peripheral blood smear [if needed];
- Serum Chemistry/Hepatic Enzymes: Glucose, Calcium, Sodium, Chloride, Albumin, Protein, Bilirubin, Lactate Dehydrogenase, AST, ALT, Potassium, Alkaline Phosphatase, BUN, Uric Acid, Creatinine, Creatine Kinase);
- Urinalysis

Tests performed at screening only:

- Serology (HIV, Hepatitis B surface antigen, Hepatitis C antibody),

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- breath alcohol test, urine cotinine, serum hCG, Urine Tests for Drugs of Abuse (marijuana, amphetamines, methamphetamines, phencyclidine, barbiturates, cocaine, opiates, benzodiazepines tetrahydrocannabinol, MDMA, and methadone).

Vital signs, ECGs, and physical and nasal examinations were performed/collected during both studies.

8.5. Safety Results

8.5.1. Deaths

No deaths were reported as of the cutoff dates for Studies 04 and 05.

8.5.2. Serious Adverse Events

A total of 39 treatment-emergent serious adverse events (TESAEs) were reported in 24 patients (14.6%) in the pooled patient safety database, primarily in patients in Study 05 (23/24, 96%). The majority of these events occurred during Study 05 (n=36), as compared to Study 04 (n=2). As seen in Table 13, seizures were the most frequent SAE, occurring in 13 patients (7.9%). The only other SAE to occur in more than 1 patient was pneumonia, which occurred in 2 patients (1.2%). The rest of the SAEs occurred in only 1 patient each. Estimation of dose effect is complicated by the small number patients in the 5 mg treatment arm. There was no clear dose effect on SAEs. No SAEs were reported in Studies 001.01, 001.02, or 001.03. The incidence of SAEs was greatest in the 6-11-year age group (23.1%), as compared to that in patients 12-17 years (13.6%) and adults (12.9%).

Table 13: Incidence of treatment emergent SAEs (primary safety dataset)

	Total (N=164)		5 mg N=3		10 mg N=38		15 mg N=52		20 mg N=72	
SAE – Preferred term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any SAE	**24**	**14.6%**	**1**	**33.3%**	**7**	**18.4%**	**10**	**19.2%**	**6**	**8.3%**
Seizure (incl status epilepticus)	13	7.9%	0		5	13.2%	5	9.6%	3	4.2%
Pneumonia	2	1.2%	0		2	5.3%	0		0	
Anterograde Amnesia	1	0.6%	0		0		1	1.9%	0	
Anxiety	1	0.6%	0		0		0		1	1.4%
Asthma	1	0.6%	0		1	2.6%	0		0	
Chest Pain	1	0.6%	0		0		0		1	1.4%
Chronic Myeloid Leukemia	1	0.6%	0		0		1	1.9%	0	
Colorectal Adenocarcinoma	1	0.6%	0		0		1	1.9%	0	
Dehydration	1	0.6%	0		0		1	1.9%	0	
Dyspnea	1	0.6%	0		0		0		1	1.4%
Encephalopathy	1	0.6%	0		0		0		1	1.4%
Hip Arthroplasty	1	0.6%	0		1	2.6%	0		0	
Hip Fracture	1	0.6%	0		0		0		1	1.4%

SAE – Preferred term	Total (N=164)		5 mg N=3		10 mg N=38		15 mg N=52		20 mg N=72	
	n	%	n	%	n	%	n	%	n	%
Large Intestinal Ulcer	1	0.6%	0		0		1	1.9%	0	
Lethargy	1	0.6%	1	33.3%	0		0		0	
Major Depression	1	0.6%	0		0		0		1	1.4%
Menorrhagia	1	0.6%	0		0		1	1.9%	0	
Pneumonia Aspiration	1	0.6%	0		1	2.6%	0		0	
Proctalgia	1	0.6%	0		0		0		1	1.4%
Psychogenic Seizure	1	0.6%	0		0		0		1	1.4%
Rectal Abscess	1	0.6%	0		0		1	1.9%	0	
Suicidal Ideation	1	0.6%	0		0		0		1	1.4%

Source: ADAE (ISS) verified in JMP

Reviewer's comment: As noted above, the most common TESAEs were seizures (14.6%) and thus related to the patients' underlying reason for treatment with IN diazepam.

In general, the SAEs reported in Studies 04 and 05 are not dissimilar from those reported in the controlled clinical trials of diazepam rectal gel. Due to the lack of a placebo comparator, and the low numbers of patients experiencing each SAE, no further conclusions on SAEs can be drawn.

One patient in Study 05 discontinued participation in the study due to SAEs. At the time of the event, subj# (b) (6) was a 44 year-old woman with a long history of refractory GTCS and a history of depression who had 6 seizures/month on average. Concurrent medications included phenytoin, levetiracetam, escitalopram, and lacosamide. She presented to an ED on study day 310 with suicidal thoughts and was admitted. The psychiatrist discontinued the DZP NS and Lexapro during the hospitalization. Nine days prior to her developing the psychiatric SAEs, the patient had taken two doses of DZP NS, and three days prior, she had taken a single dose. Her symptoms resolved by study day 316, and she was discharged. The drug was withdrawn, and she was terminated from the study on her 270-day visit.

Reviewer's comment: Of note, the Applicant did not include "Suicidal Ideation" as an SAE in the dataset; however, the narrative in the CSR states that the she was admitted to a behavioral facility after she had said "she wanted to kill herself". The safety dataset has been revised to include an SAE of suicidal ideation.

The patient had not reported any prior suicidality on the screening Columbia-Suicide Severity Rating Scale (C-SSRS); however, she had a history of depression. The contribution of the IN diazepam to the suicidal thoughts is unclear, though possible. A major confounding factor is the patient's prior history of depression.

Anti-seizure drugs have been associated with increased incidence of suicidal behavior and ideation, and these drugs carry a class warning for suicidality. Although the causal relationship between DZP NS and this patient's suicidal thoughts cannot be clearly determined, the SAE of suicidal ideation in Study 05 does not raise new concerns at this point and supports the class warning to be included in the PI.

Please see Table 14 below for a listing of all SAEs by subject in Studies 04 and 05.

Reference ID: 4544627

Table 14: Summary of SAEs (primary safety dataset)

Subj ID Age (y), Sex	Dose at SAE Onset	# Doses Received Dur Study	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Severity/ Relationship to Study Drug	Study Drug Action Taken/ Other Action Taken	Outcome
(b) (6) M	20 mg	2	Encephalopathy	7/23	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
			Seizure	40/54	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) M	20 mg	9	Seizure	10/15	Unlikely	Dose not changed/ Treatment given	Resolved
			Seizure	124/124	Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) M	10 mg	17	Seizure	7/10	Mild/Unlikely	Dose not changed/ Treatment given	Resolved
			Seizure	225/226	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
			Seizure	267/271	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) F	15 mg	3	Seizure	65/66	Mild/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) F	20 mg	30	Hip fracture	355/356 (?)	Severe/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6)	15 mg	21	Seizure	360/360	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) F	20 mg	22	Anxiety	287/295	Severe/Unlikely	Drug withdrawn/ Treatment given	Resolved
			Major Depression	287/295	Severe/Unlikely	Drug withdrawn/ Treatment given	Resolved
			Psychogenic Seizure	287/295	Severe/Unlikely	Drug withdrawn/ Treatment given	Resolved
			Suicidal Ideation	287/295	Severe/Unlikely	Drug withdrawn/ Treatment given	Resolved
(b) (6) F	15 mg	1	Chronic myelocytic leukemia	65/420	Moderate/Unlikely	Dose not changed/ Treatment given	Not Resolved

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Subj ID Age (y), Sex	Dose at SAE Onset	# Doses Received Dur Study	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Severity/ Relationship to Study Drug	Study Drug Action Taken/ Other Action Taken	Outcome
(b) (6) F	15 mg	17	Colorectal carcinoma	17/--	Severe/Unlikely		
			Large Intestinal Ulcer	198/~230	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
			Abscess	?/? (~30 days)	Severe/Unlikely	Dose not changed/ Treatment given	Recovered w/sequela
(b) (6) F	15 mg	19	Status epilepticus (Seizure)	258/259	Severe/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) F	20 mg	52	Seizure	172/176	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) F	15 mg	14	Menorrhagia	241/245	Mild/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) M	15 mg	7	Seizure	175/179	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) M	20 mg	9	Proctalgia	63/111	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
			Chest Pain	109/109	Severe/Unlikely	Dose not changed/ Treatment given	Resolved
			Dyspnea	109/109	Severe/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) M	15 mg	3	Seizure	9/9	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
			Seizure	226/231	Severe/Unlikely vs Possible	Dose not changed/ Treatment given	Resolved
(b) (6) M	7.5 mg	2	Seizure	85/87	Mild/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) F	10 mg	25	Aspiration pneumonia	267/275	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
			Pneumonia	327/336	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) F	10 mg	15	Seizure	109/110	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved

Subj ID Age (y), Sex	Dose at SAE Onset	# Doses Received Dur Study	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Severity/ Relationship to Study Drug	Study Drug Action Taken/ Other Action Taken	Outcome
(b) (6) M	10 mg	2	Seizure	140/144	Moderate/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) F	10 mg	3	Status Epilepticus (Seizure)	1/8	Mild/Unlikely	Dose not changed/ Treatment given	Resolved
			Pneumonia	47/86	Mild/Unlikely	Dose not changed/ Treatment given	Resolved
			Asthma	119/128	Mild/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) F	10 mg	11	Hip arthroplasty	176/184	/Unlikely	Dose not changed/ Treatment given	Resolved
(b) (6) M	15 mg	29	Anterograde amnesia	203/--	/Unlikely	Dose not changed/ Treatment given	Not Resolved
(b) (6) F	10 mg	2	Seizure	58/59	/Possible	Dose not changed/ Treatment given	Resolved
(b) (6) F	15 mg	4	Dehydration	45/46	/Unlikely	Dose not changed/ Treatment given	Resolved

Source: ADAE (ISS), ADSL and ADXD (Studies 04 and 05)

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8.5.3. Dropouts and/or Discontinuations Due to Adverse Effects

No patients discontinued participation in Study 04 due to adverse events. One patient discontinued participation in Study 05 due to SAEs, as summarized in Section 8.5.2 above.

8.5.4. Significant Adverse Events

One patient developed suicidal ideation while participating in Study 05. See Section 8.5.2 above for discussion.

8.5.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAEs) occurred in 94/164 (57.3%) of patients in the pooled safety database and in 28% and 49% of patients in Studies 04 and 05, respectively. A summary of the percentages of subjects with TEAEs that occurred in at least 2% of patients overall are presented in Table 15 below. The most frequently reported TEAEs were in the system organ classes (SOC) of nervous system disorders, infections and infestations, and respiratory disorders, all of which are commonly reported in this patient population.

The most frequent TEAEs in Studies 04 and 05 were seizures (any) and respiratory tract infection, which occurred in 11% and 6.1% of patients, respectively. TEAEs that occurred in at least 5% of patients in the pooled dataset from Studies 04 and 05 were seizures, somnolence/sedation/fatigue/lethargy, nasal discomfort, headache (including migraine), and upper respiratory tract infection.

Reviewer's comment: In general, other than those related to potential local effects of the IN administration, the frequently reported TEAEs are consistent both with commonly observed illnesses in this population and TEAEs observed in the controlled trials of diazepam rectal gel. See Section 8.5.4 for discussion of local effects of the IN administration of DZP NS.

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Table 15: TEAEs in ≥2% of patients by treatment arm (primary safety dataset)

	DZP NS 5 mg N=3		DZP NS 10 mg N=38		DZP NS 15 mg N=52		DZP NS 20 mg N=72		DZP NS Total N=164	
TEAE (preferred term)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any adverse event	***2***	***66.7%***	***22***	***57.9%***	***32***	***61.5%***	***38***	***52.8%***	***94***	***57.3%***
ANY LOCAL NASAL SYMPTOM (Excl Infections)	1	33.3%	3	7.9%	11	21.2%	8	11.1%	23	14.0%
Nasal Discomfort	0		0		5	9.6%	5	6.9%	10	6.1%
Nasal Congestion	0		1	2.6%	3	5.8%	1	1.4%	5	3.0%
Epistaxis	0		3	7.9%	2	3.8%	0		5	3.0%
Rhinorrhea	1	33.3%	0		1	1.9%	1	1.4%	3	1.8%
Nasal Pruritus	0		0		0		1	1.4%	1	0.6%
Nasal Ulcer	0		0		0		1	1.4%	1	0.6%
SEIZURE (Any)	0		7	18.4%	8	15.4%	3	0.4%	18	11.0%
Status Epilepticus	0		2	5.3%	1	1.9%	0		3	1.8%
Somnolence/Sedation/Fatigue/Lethargy	1	33.3%	2	5.3%	5	9.6%	2	2.8%	10	6.1%
Headache (Incl Migraine)	0		0		4	7.7%	6	8.3%	10	6.1%
Upper Respiratory Tract Infection (Incl Viral)	0		2	5.3%	3	5.8%	5	6.9%	10	6.1%
Nasopharyngitis	1	33.3%	3	7.9%	1	1.9%	3	4.2%	8	4.9%
Nausea/Vomiting	0		2	5.3%	3	5.8%	2	2.8%	7	4.3%
Dizziness	0		0		2	3.8%	4	5.6%	6	3.7%
Pyrexia	1	33.3%	4	10.5%	0		1	1.4%	6	3.7%
Influenza	0		1	2.6%	3	5.8%	1	1.4%	5	3.0%
Ataxia/Gait Disturbance/Balance Disorder	0		0		0		5	6.9%	5	3.0%
Gastroenteritis	1	33.3%	3	7.9%	1	1.9%	0		5	3.0%
Contusion	0		0		3	5.8%	1	1.4%	4	2.4%
Dysgeusia	0		0		3	5.8%	1	1.4%	4	2.4%
Fall	0		2	5.3%	1	1.9%	1	1.4%	4	2.4%
Pneumonia	0		3	7.9%	0		1	1.4%	4	2.4%
Urinary Tract Infection	0		2	5.3%	2	3.8%	0		4	2.4%
Depression	0		0		2	3.8%	2	2.8%	4	2.4%

Source: ADAE (ISS), verified in JMP

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8.5.6. Laboratory Findings

Clinical laboratory testing (hematology, serum chemistry, urinalysis, oxygen saturation, urine drug, alcohol, and tobacco screening, and pregnancy) was performed. A number of patients had reported clinical laboratory findings that were abnormal (marginally above or below the normal range). However, the majority of these were considered not clinically significant, single findings, observed during the screening, or observed at baseline.

Reviewer's Comments: Review of the clinical laboratory data did not identify any safety signal.

8.5.7. Vital Signs

Vital signs were assessed periodically during Studies 04 and 05. No clinically significant findings were reported.

8.5.8. Electrocardiograms (ECGs)

ECGs were assessed periodically during Studies 04 and 05. No clinically significant findings were reported.

8.5.9. QT

No QT prolongation was reported during the development program.

8.5.10. Immunogenicity

Not applicable.

8.6. Analysis of Submission-Specific Safety Issues

8.6.1. Nasal and Olfactory Toxicity

Nasal and olfactory toxicity were of special interest in this development program. Changes to olfaction and local toxicity to the nasopharynx were prospectively evaluated in Studies 04 and 05. In Study 04, olfaction was assessed at baseline, at several timepoints post-dose, and at discharge. No formal statistical analyses were performed on these outcome measures. In Study 05, olfaction was assessed at baseline, at several visits during the course of the study, and at discharge. No formal statistical analyses were performed on these outcome measures.

In Study 04, no clinically meaningful mean changes from baseline on the NIH Toolbox Odor Identification Test scores were identified. In the prospective assessments of nasal irritation, only one moderate finding was reported (1 patient was noted to have moderate mucosal erythema on one occasion). All other changes were mild and occurred in only a few patients.

Nasal mucosal pain was assessed using a Visual Analog Scale (VAS) score. Mean VAS scores changed slightly in the Study 04 population post-dose compared to baseline, although these changes were not considered to be clinically significant.

In Study 05, there were no clinically meaningful mean changes from baseline on the NIH Toolbox Odor Identification Test scores. There were no clinically significant findings on the assessments of nasal irritation. No dose-related trends in nasal irritation results or changes from just prior to dosing to post dose were identified. All reported findings were mild.

Local toxicity was also assessed by the incidence of TEAEs that were either identified in the verbatim terms as being associated with drug administration or are reasonably considered to be associated with the administration. As seen in Table 16 below, 70 local AEs occurred in 30/164 patients (18.3%) during Studies 04 and 05. Such events included nasal discomfort (6.1%), nasal congestion (3%), epistaxis (3%), dysgeusia (2.4%), rhinorrhea (1.8%), cough (1.8%), eye irritation (1.2%), increased lacrimation (1.2%), and oropharyngeal pain (1.2%). Nasal pruritus, nasal ulcer, dysphonia, ocular hyperemia, mucosal edema, retching, sneezing, and throat irritation were each reported in 1 patient (a total of 6 patients affected, each having 1 or 2 of these local AEs). There was no clear relationship to dose.

Overall the incidences of local AEs were similar in all age groups (adult: 19.8%, adolescents: 13.6%, and children 15.4%). Some events, such as nasal discomfort, were more frequently seen in adults (8.6%) than in children (0%) or adolescents (0%). Others, such as epistaxis, were seen more frequently in children (7.7%) and adolescents (9.1%) than in adults (0.9%).

Reviewer's Comments: No clinically meaningful changes or findings were observed in the prospective assessments of olfaction and nasal toxicity in either study. Overall, local adverse events related to nasal administration of diazepam occurred in more than 18% of patients in the pooled Studies 04 and 05 dataset. However, all of these events were characterized as mild in severity and none led to discontinuation or dose adjustment. There was no overall correlation of local AEs to dose or age group. Based on the safety data from Studies 04 and 05, there is no safety signal for local nasal toxicity of DZP NS, when used in a chronic intermittent fashion in patients with ARS.

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Table 16: Incidence of local TEAEs related to intranasal administration of DZP NS (primary safety dataset)

Preferred Term	DZP NS 5 mg (n=3)		DZP NS 10 mg (n=38)		DZP NS 15 mg (n=52)		DZP NS 20 mg (n=72)		DZP NS Total (n=164)		6 to <12 yrs (n=22)		12 to <18 yrs (n=22)		≥18 yrs (n=116)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Events (#)	1		5		30		34		70		5		4		61	
Any Local Ocular/Oral/Nasal Symptom (Excl Infections)	**1**	**33.3%**	**4**	**10.5%**	**14**	**26.9%**	**11**	**15.3%**	**30**	**18.3%**	**4**	**15.4%**	**3**	**13.6%**	**23**	**19.8%**
Nasal Discomfort	0		0		5	9.6%	5	6.9%	10	6.1%	0		0		10	8.6%
Epistaxis	0		3	7.9%	2	3.8%	0		5	3.0%	2	7.7%	2	9.1%	1	0.9%
Nasal Congestion	0		1	2.6%	3	5.8%	1	1.4%	5	3.0%	1	3.8%	1	4.5%	3	2.6%
Dysgeusia	0		0		3	5.8%	1	1.4%	4	2.4%	0		0		4	3.4%
Cough	0		0		1	1.9%	2	2.8%	3	1.8%	0		0		3	2.6%
Rhinorrhea	1	33.3%	0		1	1.9%	1	1.4%	3	1.8%	1	3.8%	0		2	1.7%
Eye Irritation	0		1	2.6%	0		1	1.4%	2	1.2%	1	3.8%	0		1	0.9%
Increased Lacrimation	0		0		2	3.8%	0		2	1.2%	0		0		2	1.7%
Oropharyngeal Pain	0		0		2	3.8%	0		2	1.2%	0		0		2	1.7%
Dysphonia	0		0		0		1	1.4%	1	0.6%	0		0		1	0.9%
Nasal Pruritus	0		0		0		1	1.4%	1	0.6%	0		0		1	0.9%
Nasal Ulcer	0		0		0		1	1.4%	1	0.6%	0		0		1	0.9%
Ocular Hyperemia	0		0		0		1	1.4%	1	0.6%	0		0		1	0.9%
Mucosal Edema	0		0		0		1	1.4%	1	0.6%	0		0		1	0.9%
Retching	0		0		0		1	1.4%	1	0.6%	0		0		1	0.9%
Sneezing	0		0		1	1.9%	0		1	0.6%	0		1	4.5%	0	
Throat Irritation	0		0		0		1	1.4%	1	0.6%	0		0		1	0.9%

Source: ADAE (AEDECOD by USUBJID and AGE or DOSE GROUPS) with recoding, ISS dataset

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8.7. Safety Analyses by Demographic Subgroups

TEAEs by age

When TEAEs were considered by age subgroups (6 to < 12 years, 12 to < 18 years, and ≥18 years) in the pooled dataset, there were no clear patterns of distribution (Table 17). Overall, AEs were more commonly seen in children (65%) and adolescents (59%) than in adults (55%), but the differences in incidences were relatively small. Some events were more frequently observed in the younger pediatric patients than in adolescents or adults, such as somnolence/sedation/fatigue/lethargy (12%, 9%, 4%), seizures (24%, 14% and 8%), respiratory tract infection (15%, 0%, and 6%), nausea/vomiting (15%, 0%, and 3%), and nasopharyngitis (12%, 5%, and 3%). Other events were seen more frequently in adults than in adolescents or children: nasal discomfort (8.6%, 0%, and 0%), headache (9%, 0%, and 0%), and dizziness (5%, 0%, and 0%).

Table 17: TEAEs by age group (in at least 3 patients), primary safety dataset

	Total (n=164)		Age 6 to <12 years (n=26)		Age 12 to <18 years (n=22)		Age ≥18 years (n=116)	
TEAEs (preferred term)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any TEAE	***94***	***58%***	***17***	***65%***	***13***	***59%***	***64***	***55%***
Seizure	18	11%	6	24%	3	14%	9	8%
Respiratory Tract Infection	11	7%	4	15%	0		7	6%
Headache	10	6%	0		0		10	9%
Nasal Discomfort	10	6%	0		0		10	9%
Somnolence/Sedation/ Fatigue/Lethargy	10	6%	3	12%	2	9%	5	4%
Nasopharyngitis	8	5%	3	12%	1	5%	4	3%
Nausea/Vomiting	7	4%	4	15%	0		3	3%
Dizziness	6	4%	0		0		6	5%
Pyrexia	6	4%	2	8%	2	9%	2	2%
Ataxia/Gait Disturbance/ Balance Disorder	5	3%	0		0		5	4%
Epistaxis	5	3%	2	8%	2	9%	1	1%
Gastroenteritis	5	3%	2	8%	0		3	3%
Influenza	5	3%	2	8%	0		3	3%
Nasal Congestion	5		1	4%	1	5%	3	3%
Contusion	4	2%	0		0		4	3%
Depression	4	2%	1	4%	0		3	3%
Dysgeusia	4	2%	0		0		4	3%
Fall	4	2%	1	4%	1	5%	2	2%
Pneumonia	4	2%	2	8%	1	5%	1	1%
Urinary Tract Infection	4	2%	1	4%	0		3	3%
Cough	3	2%	0		0		3	3%
Laceration	3	2%	3	12%	0		0	

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TEAEs (preferred term)	Total (n=164)		Age 6 to <12 years (n=26)		Age 12 to <18 years (n=22)		Age ≥18 years (n=116)	
	n	%	n	%	n	%	n	%
Otitis Media	3	2%	1	4%	0		2	2%
Rhinorrhea	3	2%	1	4%	0		2	2%
Status Epilepticus	3	2%	1	4%	1	5%	1	1%
Weight Increased	3	2%	0		0		3	3%

Source: pooled ADAE (AEDECOD by USUBJID and AGE)

Reviewer's comment: Although some differences in the incidence of AEs were observed between age groups, the clinical significance of these differences is unclear, due to the relatively small sample sizes of the pediatric age groups and the lack of a placebo comparator.

TEAEs by dose

As these were open-label studies, assessment of TEAEs by dose was not possible. As noted above in Section 8.5.5, there appeared to be a dose effect with some adverse events, but many AEs were not associated with this effect.

8.8. Specific Safety Studies/Clinical Trials

Not applicable

8.9. Additional Safety Explorations

8.9.1. Human Carcinogenicity or Tumor Development

Data is reliant on the listed drug.

8.9.2. Human Reproduction and Pregnancy

Data is reliant on the listed drug.

8.9.3. Pediatrics and Assessment of Effects on Growth

Data is reliant on the listed drug.

8.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data is reliant on the listed drug. Please also see full CSS review.

As listed in the Diastat label, "Chronic daily use of [redacted] (b) (4) may increase the frequency and/or severity of tonic-clonic seizures, requiring an increase in the dosage of standard

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anticonvulsant medication. In such cases, abrupt withdrawal of chronic (b) (4) may also be associated with a temporary increase in the frequency and/or severity of seizures."

Reviewer's comment: Patients in Study 05 did not take DZP NS more frequently than every 3 days. The above statement from the Diastat label on chronic use and concern for tolerance and withdrawal symptoms represents a class effect and should be included in the DZP NS label as well. There are no data to support that DZP NS is any safer in that regard than use of rectal diazepam. It is recommended that DZP NS not be used to treat more than 5 seizure episodes in a month or more frequently than every 5 days.

8.10. Safety in the Postmarket Setting

There is no postmarket experience of this drug product. There are well-established safety issues present in the listed drug labeling from prior experience with diazepam rectal gel and in other formulations, routes of administrations, and indications. Review of the 120-day safety update did not raise any new safety signals.

8.11. Integrated Assessment of Safety

This review summarizes the safety data collected primarily from 164 patients with epilepsy exposed to diazepam nasal spray in one comparative bioavailability study and one open-label, long-term safety study. The clinical safety tests conducted in the studies were appropriate and capable of identifying major safety signals. Overall, the safety findings from this submission are consistent with data from the original NDA submission for diazepam rectal gel (Diastat). No new safety signals were identified in either Study 04 or Study 05, or in the rest of this product's development program. No evidence of local nasal or olfactory toxicity was identified in Studies 04 and 05.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee was not considered necessary.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The labeling has not been finalized as of the time of this review.

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10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS was deemed unnecessary.

12. Postmarketing Requirements and Commitments

The necessity of post-marketing requirements or commitments has not been determined at the time of this review.

13. Appendices

13.1. References

See footnotes throughout the review.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): DIAZ.001.01, DIAZ.001.02, DIAZ.001.03, DIAZ.001.04, DIAZ.001.05

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 33		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

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54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Reference ID: 4544627

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/s/

NATALIE B GETZOFF
01/10/2020 09:59:38 AM

PHILIP H SHERIDAN
01/10/2020 11:08:12 AM