CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211635Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA Number	211635
Link to EDR	\\CDSESUB1\evsprod\NDA211635
Submission Date	9/20/2018
Submission Type	505(b)(2) NDA
Brand Name	VALTOCO
Generic Name	Diazepam
Dosage Form and Strength	Nasal Spray (50 mg/mL, 75 mg/mL and 100 mg/mL)
Route of Administration	Nasal
Proposed Indication	For 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)
Applicant	Neurelis, Inc.
OCP Review Team	Jagan Mohan Parepally, Ph.D., Angela Men, M.D., Ph.D.

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1. EXECUTIVE SUMMARY

This is a 505(b)(2) New Drug Application (NDA) to support the marketing approval of Valtoco™ (diazepam, nasal spray) for 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), using Diastat® (diazepam rectal gel) as listed drug (LD). Diazepam is a benzodiazepine and acts through potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABAA receptor. At present, Diastat® (diazepam rectal gel) is the only product approved for this indication. Diazepam Nasal Spray is a nonaqueous solution for intranasal administration via standard commercially available Unit Dose nasal sprayer. Product would deliver 5 mg, 7.5 mg or 10 mg per actuation.

The clinical development program includes four Phase 1 studies and a safety and usability study. There are no efficacy trials conducted to support this application. These four Phase 1 studies included a pivotal relative bioavailability study that compared Valtoco to Diastat®, a dose proportionality study, a pharmacokinetic (PK) study comparing epilepsy patients between ictal/peri-ictal and interictal states to detect possible differences in absorption due to changes in breathing patterns and obtundation. Safety and usability study was a 12-month study to assess the safety of diazepam after repeat intranasal doses of Valtoco 5 mg, 10 mg, 15 mg, or 20 mg administered based on the subject's age and body weight in epilepsy patients.

A consult was sent to the Office of Study Integrity and Surveillance (OSIS) requesting inspections of clinical and analytical sites of pivotal relative bioavailability study DIAZ.001. The OSIS concluded that the data are acceptable based on the records of recent inspections of the study sites.

1.1 Recommendations

The office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 211635. The information provided supports the approval of Valtoco for 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). Key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness and safety	The exposures and pharmacokinetic profiles after administration of Valtoco (diazepam NS) are within the range of Diastat® (diazepam rectal gel) PK profiles; therefore, the efficacy and safety profiles following the treatment of Valtoco should be similar to those of the approved Diastat® (see section 3.3.1).
General dosing instructions	The dosing instruction are similar to that of LD, Diastat and acceptable (i.e., body weight-based dosing). The initial dose of diazepam as nasal spray 5 mg and 10 mg doses are administered as a single spray intranasally into one nostril. Administration of 15 mg

	and 20 mg doses requires two nasal spray devices, one spray into each nostril. A second dose may be administered 4 to 12 hours after first dose if seizure activity continues using a new pack (see section 3.3.3).
Dosing in patient subgroups (intrinsic and extrinsic factors)	The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Valproate and alcohol may potentiate the CNS-depressant effects of diazepam.
Labeling	General dosing recommendations are acceptable.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation and delivery device, referred to as Valtoco in this submission, were used in all clinical studies.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Diazepam is a compound of the benzodiazepine class. The exact mechanism of action for diazepam is not fully understood, but it is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABAA receptor. GABA, the major inhibitory neurotransmitter in the central nervous system, acts at this receptor to open the membrane channel allowing chloride ions to flow into neurons. Entry of chloride ions causes an inhibitory potential that reduces the ability of neurons to depolarize to the threshold potential necessary to produce action potentials.

The absolute bioavailability (BA) was approximately 97% for Valtoco. In an ascending dose PK study in adults, median time to maximum concentration (Tmax) following nasal administration of Valtoco was approximately 1.5 hours. The mean elimination half-life of diazepam following administration of a 10 mg dose of Valtoco nasal spray was found to be about 49.2 hours. The PK parameters of diazepam and nordiazepam following diazepam nasal spray administration were found to be essentially proportional (Study DIAZ.001.02). The PK data was comparable in epilepsy patients between ictal/peri-ictal and interictal states (to detect possible differences as a result of factors such as changes in breathing patterns and obtundation).

2.1.1 Pharmacokinetic comparison of diazepam between nasal spray (Valtoco®), rectal gel (Diastat®) and IV Administration

In a pivotal relative BA study DIAZ.001.03, an open-label, randomized, single-dose, three-treatment, three-period, six-sequence crossover study diazepam and nordiazepam exposure (Cmax and AUCs) was evaluated following 15 and 20 mg using nasal spray (Valtoco) and listed drug, Diastat® (diazepam rectal gel). Body weight was taken into consideration per Diastat prescribing information for 15 or 20 mg diazepam dose. The diazepam PK parameters were less variable for Valtoco (2 to 4-fold lower) and within the range of those seen with Diastat. For 15 mg treatment group, the geometric mean ratio (GMR) for Cmax was 85% and 90% confidence intervals (90% CIs) ranged from 57% to 126%. The GMR for AUC0-∞ was 74% and 90% CIs

ranged from 53% to 102%. For 20 mg treatment group, the GMR for Cmax was 118% and 90% CIs ranged from 69% to 202%. The GMR for AUC0-∞ was 100% and 90% CIs ranged from 65% to 152%. The shape of the pharmacokinetic profiles was also similar. Therefore, the efficacy of Valtoco would be expected to be similar to that of LD (see section 3.3.1).

The PK comparison between the proposed to-be-marketed formulation and the approved diazepam IV formulation was evaluated in study DIAZ.001.01. At a dose of 10 mg, the absolute bioavailability of the to-be-marketed formulation was 97% compared to the approved IV formulation (see section 3.3.8).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The initial dose of diazepam as nasal spray 5 mg and 10 mg doses are administered as a single spray intranasally into one nostril. Administration of 15 mg and 20 mg doses requires two nasal spray devices, one spray into each nostril. A second dose may be administered 4 to 12 hours after first dose if seizure activity continues using a new pack.

2.2.2 Therapeutic individualization

No new drug-drug interaction studies were conducted for this application. The sponsor relies on LD for appropriate management strategy. The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Valproate and alcohol may potentiate the CNS-depressant effects of diazepam. (b) (4)

2.4 Summary of Labeling Recommendations

The proposed labeling language including (b) (4) in Section 12.3 of labeling should be deleted and replaced with statements consistent with the other 505(b)(2) applications. Proposed labeling language related to drug-drug interactions from LD should be consistent with labeling guidance.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The applicant (Neurelis, Inc.) has developed diazepam nasal spray formulation (Valtoco 50 mg/mL, 75 mg/mL and 100 mg/mL) and is seeking approval for intermittent use in adults and children six years and older with epilepsy, on stable regimens of AEDs, to control bouts of increased seizure activity, often referred to as cluster or ARS. The intranasal delivery is provided by using a standard commercially available Unit Dose nasal sprayer (Aptar Pharma, formerly

Pfeiffer). Following inactive ingredients are included in single dose spray dispensor: α-tocopherol, Intravail® A3 (dodecylmaltoside) benzyl alcohol and (b) (4)

Regulatory interactions contributing to clinical pharmacology program included recommendations to evaluate intra-patient comparison of PK data between ictal/peri-ictal and interictal states (to detect possible differences as result of factors such as changes in breathing patterns and obtundation). To develop a weight-based dosing regimen equivalent to the Diastat prescribing information. To include adequate number of pediatric patients to support safety and comparative bioavailability in patients 6 years of age and younger.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	The exact mechanism of action for diazepam is not fully understood, but it is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABAA receptor. GABA, the major inhibitory neurotransmitter in the central nervous system, acts at this receptor to open the membrane channel allowing chloride ions to flow into neurons. Entry of chloride ions causes an inhibitory potential that reduces the ability of neurons to depolarize to the threshold potential necessary to produce action potentials.
General Information	
Bioanalysis	Plasma diazepam and its active metabolite nordiazepam concentrations were measured by a validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods. Diazepam-d5 and nordiazepam-d5 were used as the internal standards. The lower limit of quantitation was 1 ng/mL and 100 pg/mL respectively for both analytes.
Healthy Volunteers vs Patients	A cross study comparison of diazepam Cmax and AUC0-6 in epileptic patients to that of normal healthy subjects indicated that patients with epilepsy had lower AUC (~ 25% to 33%) and Cmax (~34% to 42%) levels of diazepam compared to healthy subjects (Study DIAZ.001.04).
Dose Proportionality	The PK parameters of diazepam and nordiazepam following diazepam nasal spray administration were found to be essentially proportional (Study DIAZ.001.02) between 5 and 20 mg. All PK parameters were similar across cohorts and did not exhibit dose dependent changes (see section 3.3.6).
ADME	
Absorption	Median time to maximum concentration (Tmax) following nasal administration of Valtoco was approximately 1.5 hours. The mean absolute bioavailability is approximately 97%.
Distribution	The estimated volume of distribution of diazepam is approximately at steady-state is 0.8 to 1.0 L/kg. Both diazepam and its major active metabolite desmethyldiazepam bind extensively to plasma proteins (95-98%).

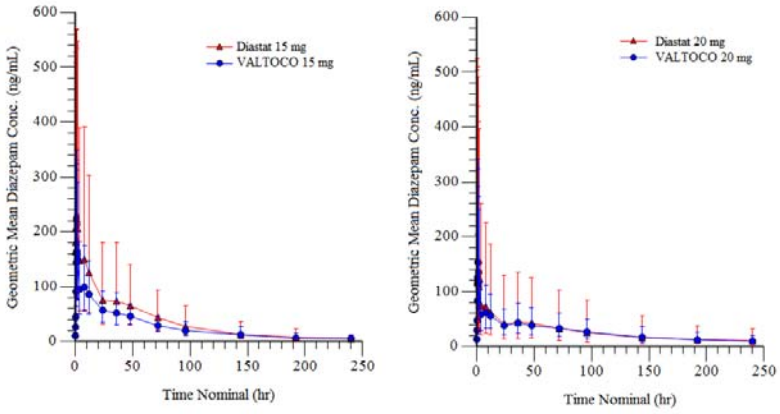
Metabolism	Diazepam is extensively metabolized to one major active metabolite (desmethyldiazepam) and two minor active metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam) in plasma. At therapeutic doses, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam while oxazepam and temazepam are not usually detectable. The metabolism of diazepam is primarily hepatic and involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation (involving primarily CYP3A4), followed by glucuronidation.
Elimination	The mean elimination half-life of diazepam following administration of a 10 mg dose of Valtoco nasal spray was found to be about 49.2 hours. However, nordiazepam has a half-life of 40-99 hours according to the literature.

3.3 Clinical Pharmacology Review Questions

3.3.1 Is an adequate bridge established between Valtoco and the listed drug Diastat rectal gel? Is there a significant pharmacokinetic difference of diazepam between nasal spray (Valtoco®) and rectal gel (Diastat®) Administration?

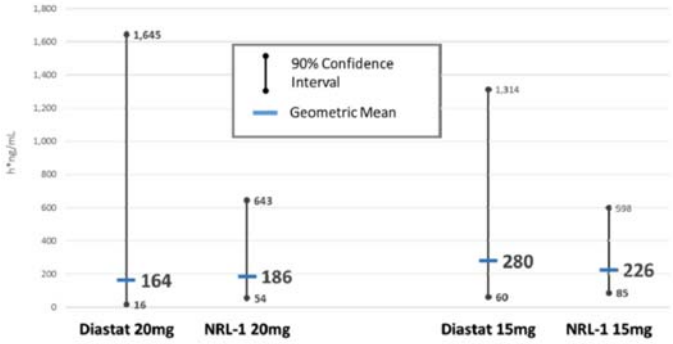
In a relative BA study DIAZ.001.03, an open-label, randomized, single-dose, three-treatment, three-period, six-sequence crossover study diazepam and nordiazepam exposure (Cmax and AUCs) was evaluated following 15 and 20 mg using nasal spray (Valtoco) and listed drug, Diastat® (diazepam rectal gel). Body weight was taken into consideration per Diastat prescribing information for 15 or 20 mg diazepam dose. Following figure represents mean plasma diazepam concentration-time profiles per treatment.

Mean Plasma Concentration-Time Profiles of Diazepam, 15 and 20 mg VALTOCO Nasal Spray and 15 and 20 mg Diazepam Rectal Gel (Geometric Mean with Upper and Lower 1 Geometric Deviation)



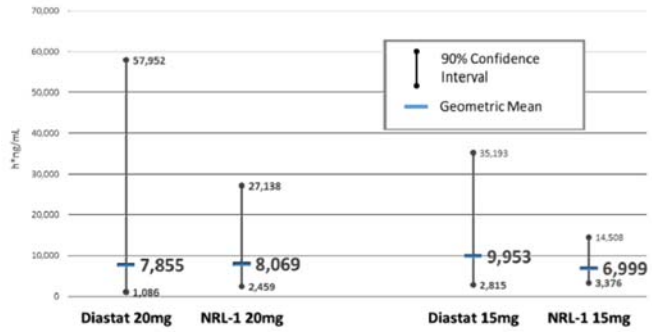
The comparison of these products show that diazepam PK parameters were less variable for Valtoco (2 to 4-fold lower) and within the range of those seen with Diastat as shown in figures below.

Comparative Pharmacokinetic Measures: Cmax



Note: The high-weight subjects showed greater variability compared to the low-weight subjects when diazepam was administered by different routes. Compared to Diastat, intranasal administration of NRL-1 resulted in comparable AUC0-∞ values based on geometric mean values at the 20mg dose but was lower than Diastat at the 15mg dose. This result was apparently due to the more significant impact of body weight and BMI on the exposure of diazepam when administered rectally, which resulted in persons in the 50 kg to 75 kg group given a 15 mg dose having a much higher AUC than those subjects in the greater than 75 kg group who received a 20 mg dose.

Comparative Pharmacokinetic Measures: AUC0-∞



A comparison of diazepam Cmax and AUC between 15 mg and 20 mg Valtoco and 15 mg Diastat are presented in Tables below.

Comparison of Diazepam Cmax and AUC between 15 mg VALTOCO and 15 mg Diastat

Wt Group	Dependent	Ratio %Ref	CI 90 Lower	CI 90 Upper
Low (N=17)	Ln(Cmax)	85	57	126
	Ln(AUC0-∞)	74	53	102

CI = confidence interval, Ref = reference, Wt = weight

Comparison of Diazepam Cmax and AUC between 20 mg VALTOCO and 20 mg Diastat

Wt Group	Dependent	Ratio %Ref	CI 90 Lower	CI 90 Upper
High (N=28)	Ln(C_{max})	118	69	202
	Ln($AUC_{0-\infty}$)	100	65	152

CI = confidence interval, Ref = reference, Wt = weight

To compare $AUC_{0-\infty}$, and Cmax between the proposed to-be-marketed nasal spray formulation and listed drug, Diastat® (diazepam rectal gel) analysis of variance (ANOVA) was used. For 15 mg treatment group, the geometric mean ratio (GMR) for Cmax was 85% and 90% confidence intervals (90% CIs) ranged from 57% to 126%. The GMR for AUC0-∞ was 74% and 90% CIs ranged from 53% to 102%. For 20 mg treatment group, the GMR for Cmax was 118% and 90% CIs ranged from 69% to 202%. The GMR for AUC0-∞ was 100% and 90% CIs ranged from 65% to 152% as shown in tables above.

Note: Because of high variability in diazepam exposure and body weight-based dosing the Diastat USPI recommends 'acceptable weight ranges for each dose and age category, such that patients will receive between 90% and 180% of the calculated recommended dose'.

The GMR in PK parameters was close to 100% in 20 mg treatment group possibly because of higher number of subjects (n=28) when compared to 15 mg (n=17). The shape of the pharmacokinetic profiles was also similar. Therefore, the efficacy of Valtoco would be expected to be similar to that of rectal gel (Diastat®).

3.3.2 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

This is a 505(b)(2) application for diazepam nasal spray using Diastat® (diazepam rectal gel) as LD. The efficacy of diazepam nasal spray was relied on previous findings for LD.

The applicant conducted a pivotal relative BA study (DIAZ.001.03) to support PK bridging between Valtoco and the LD, Diastat (see section 3.3.1). The supportive studies including an absolute BA study (DIAZ.001.01) comparing early formulations of diazepam NS to IV diazepam, a dose proportionality study comparing single doses (5 mg, 10 mg and 20 mg) and two doses (10 mg, 4 hour apart) of diazepam after administration of Valtoco to healthy subjects (DIAZ.001.02) and a PK study in epilepsy subjects under seizure and normal conditions (n=25, DIAZ.001.04).

3.3.3 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is acceptable. The proposed dose of Valtoco nasal spray 5 mg and 10 mg doses are administered as a single spray intranasally into one nostril. Administration of 15 mg and 20 mg doses requires two nasal spray devices, one spray into each nostril. A second dose may be administered 4 to 12 hours after first dose if seizure activity continues using a new pack (DIAZ.001.05). A second dose is also allowed to be administered with-in 4 to 12 hours per LD's approved labeling. The following table provides the acceptable weight ranges for each dose and age category, such that patients will receive between 90% and 180% of the calculated recommended dose. The proposed dose is similar to Diastat dosing recommendation based on body weight and age range. The body weight ranges in each group (6- 11 years and 12+ years) includes four subgroups instead of 7 in Diastat. The additional intermediate dosing brackets in Diastat (7.5 mg, 12.5 mg and 17.5 mg) are not available for Valtoco. Fewer subgroups were included because for lower variability of diazepam PK following the administration of Valtoco. The safety of this dosing strategy has been established in clinical trial (DIAZ.001.05). Though the number of subjects in 6 to 11 years old subgroup are low (n=14) additional safety data from study DIAZ001.04 was considered.

6 – 11 years (0.3mg/kg) N=14	
Weight (kg)	**Dose (mg)**
10 - 18	5
19 - 37	10
38 - 55	15
56 - 74	20

12+ years (0.2mg/kg) N=95	
Weight (kg)	**Dose (mg)**
14 - 27	5
28 - 50	10
51 - 75	15
76 and up	20

3.3.4 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. Based on the information currently in the label for the LD, dose adjustment is not required due to intrinsic factors.

3.3.5 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food effect was not evaluated on the proposed nasal formulation because of the route of administration and the proposed indication, acute treatment of seizures in patients who require

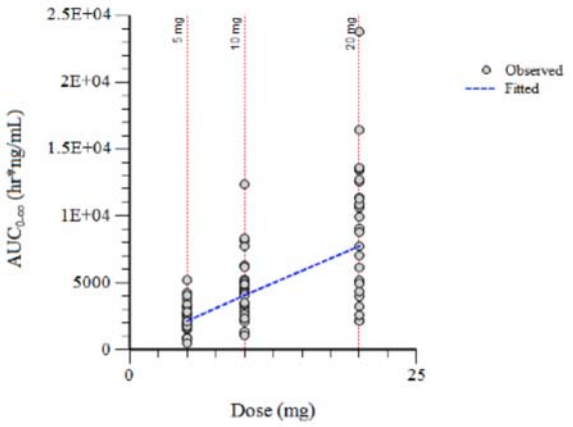
control of intermittent episodes of increased seizure activity. There is a potential for part of the drug administered to nasal cavity be absorbed though gastro intestinal tract.

No new drug-drug interaction studies were conducted for this application. The sponsor relies on LDs for appropriate management strategy.

3.3.6 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Diazepam and nordiazepam exposure increased essentially proportionally with increasing diazepam nasal spray dose of 5 mg, 10 mg and 20 mg in healthy subjects (DIAZ.001.02) as shown in the figure below.

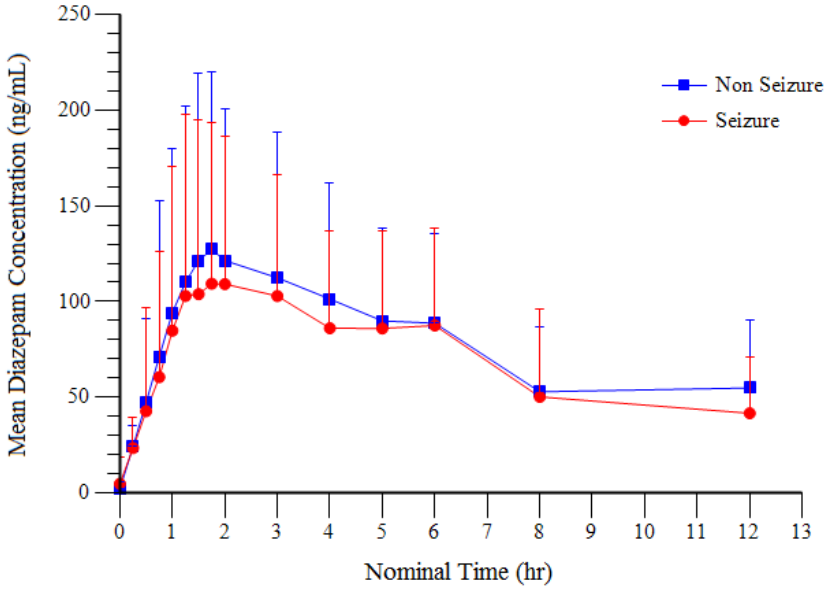
Plot of Diazepam AUC0-∞ versus Dose (Single Dose)



3.3.7 Are there any differences in absorption of diazepam in epilepsy subjects during the ictal or peri-ictal period when compared to normal conditions following administration of Valtoco?

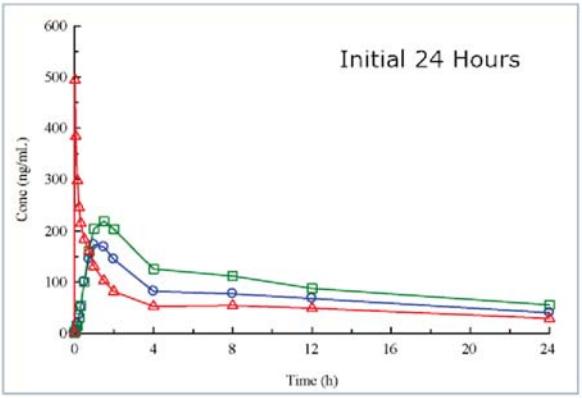
A clinical trial (DIAZ.001.04) was conducted to evaluate differences in the absorption of diazepam following administration of Valtoco in epilepsy subjects during the ictal or peri-ictal period when compared to normal conditions. The mean PK profiles were similar with a large overlap following intra nasal administration of Valtoco in patients during seizure (ictal or periictal) or non-seizure (normal state) as shown in the figure below.

Mean Plots of the VALTOCO Nasal Spray Plasma Concentration versus Time Curves: Separated by Condition



3.3.8 What is the absolute bioavailability of Valtoco?

A three-Period, three-treatment, six-sequence randomized crossover clinical trial was conducted to evaluate the bioavailability (DIAZ.001.01) was conducted using Valtoco, IV diazepam and earlier suspension formulation in healthy subjects. Diazepam was extensively absorbed after intranasal administration of non-aqueous solution (Valtoco) with an absolute bioavailability of 97% with a median Tmax of 1.5 hours as shown in the figure below. Blood samples were collected upto 240 hours (see section 4.21) for further details.



Red PK profile: IV diazepam
Green PK profile: Valtoco
Blue PK profile: Earlier suspension formulation

4. APPENDICES

4.1: Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

A validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of plasma diazepam and its active metabolite nordiazepam concentrations. Diazepam-d5 and nordiazepam-d5 were used as the internal standards. The lower limit of quantitation was 1 ng/mL and 100 pg/mL respectively for both analytes. Following table describes the summary of method validation and performance.

Table 3: Summary of Bioanalytical Method Validation and Performance

Full Validation Report Title:	Validation of a High-Performance Liquid Chromatographic Method using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Diazepam (1 to 1000 ng/mL) and Nordiazepam (100 to 100000 pg/mL) in Human EDTA K_2 Plasma
Validation Calibration Range:	1.00 to 1000.00 ng/mL for diazepam (A) and 100.00 to 100000.00 pg/mL for nordiazepam (B) (refer to the validation report in section 16.2.5.3 including the raw numerical data and also including the "Bioanalytical QC Statement Authorizing Sample Analysis" form)
Between-Run Accuracy and Precision:	A: Biases: -0.10 to 3.89% CV: 1.39 to 3.99% B: Biases: -3.14 to -0.48% CV: 1.68 to 5.88%
Within-Run Accuracy and Precision:	A: Biases: -1.59 to 4.67% CV: 1.45 to 4.59% B: Biases: -4.42 to 3.60% CV: 1.19 to 6.86%
Freeze and Thaw Stability:	4 cycles at -20°C
Short-Term Stability of Analyte in Matrix:	24h30min at 4ºC
Long-Term Stability of Analyte in Matrix:	133 days at -20°C
Post-Preparative Stability:	97h05min at room temperature

Maximum Run Size: 288 samples

A consult was sent to the Office of Study Integrity and Surveillance (OSIS) requesting inspections clinical and analytical sites of pivotal relative bioavailability study DIAZ.001. The OSIS concluded that the data are acceptable based on the records of recent inspections of the study sites.

4.2 Clinical Pharmacokinetics

4.2.1 Individual Study Reports

DIAZ.001.01: A Three-Period, Three-Treatment, Six-Sequence Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Diazepam After Intranasal and Intravenous Administration to Healthy Volunteers Under Fasted Conditions

Objectives:

Primary:
To assess the bioavailability and pharmacokinetics (PK) of diazepam after intranasal administration of suspension and solution formulations compared to intravenous (IV) administration to healthy volunteers under fasted conditions.

Secondary:
To assess the safety and tolerability of two formulations of diazepam nasal spray after a single intranasal administration of each formulation.

Study Design	This study was an open-label, randomized, three-treatment, three-period, six-sequence crossover study to evaluate the PK of diazepam after administration of an intranasal suspension (NRL-1.A), 10 mg, or an intranasal solution (NRL-1.B), 10 mg, compared to 5 mg administered by IV. Each diazepam dose was separated by a minimum 14-day washout period.
Study Population	Healthy Subjects (males and female) Age: 18-45 years BMI: 18 to 32 kg/m2 24 subjects were enrolled and 24 completed the study
Treatments	• Diazepam nasal spray, suspension (NRL-1.A), single 10-mg intranasal dose • Diazepam nasal spray, solution (NRL-1.B), single 10-mg intranasal dose • Diazepam IV, 5 mg/mL, administered over 1 minute

<table>
<tr><td>Analysis</td><td>A validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of plasma diazepam and its active metabolite nordiazepam concentrations. Diazepam-d5 and nordiazepam-d5 were used as the internal standards. The lower limit of quantitation was 1 ng/mL and 100 pg/mL respectively for both analytes. Following table describes the summary of method validation and performance. Summary of control results are presented in the table below.

Diazepam
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>3.0, 60 and 800 ng/mL</td><td>1.0, 2.0, 20, 100, 200, 400, 800 and 1000 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>3.80 to 4.72</td><td>2.00 to 3.84</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-2.83 to -0.875</td><td>-2.90 to 3.84</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.9991</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">1 to 1000 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">1 ng/mL</td></tr>
</table></td></tr>
<tr><td>Pharmacokinetic Assessments</td><td>Pharmacokinetic parameters were calculated using noncompartmental analysis. Only plasma concentrations that were ≥ LOQ for the assay (0.1 ng/mL for both diazepam and desmethyldiazepam) were used in the PK analysis. The following single-dose PK parameters were derived from the plasma concentrations of diazepam and desmethyldiazepam collected during each dose period: the maximum plasma concentration (Cmax), time to Cmax (Tmax), elimination rate constant, elimination half-life (t1/2), areas under the concentration-time curve (AUC) to the final sample (AUC0-t) and to infinity (AUC0-inf).

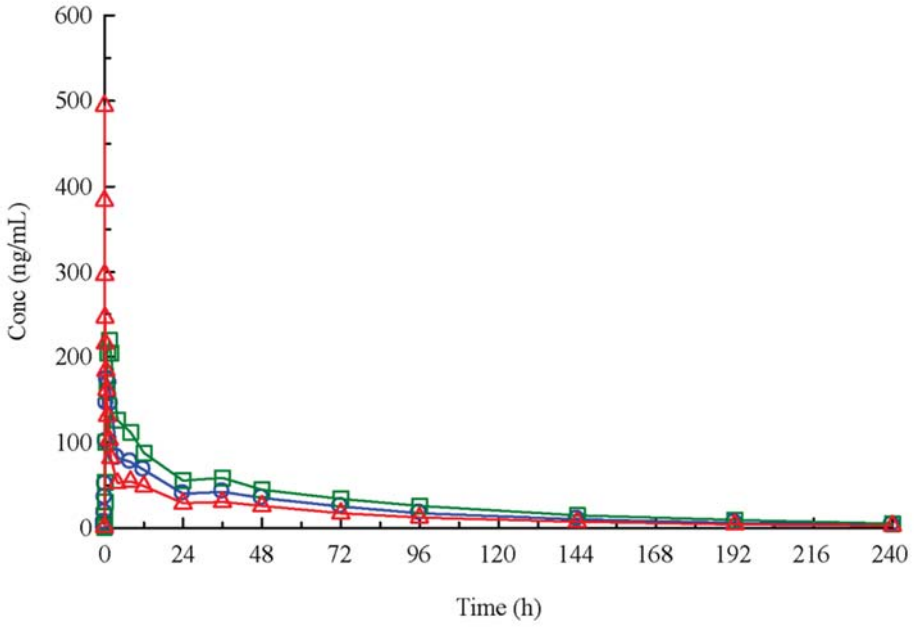
Blood samples for the measurement of plasma concentrations of diazepam and desmethyldiazepam were collected immediately prior to dosing, 7 times within the first hour after dosing (i.e., at 2.5, 5, 10, 15, 20, 30, and 45 minutes postdose); and at 1, 1.5, 2, 4, 8, 12, and 24 hours postdose (with “postdose” to mean the start of the IV diazepam infusion or after an intranasal dose). Subjects were discharged from the study center following completion of the 24-hour postdose blood sample and returned on an outpatient basis (on Days 3 through 11) for the 36-, 48-, 60-, 72-, 96-, 144, 192-, and 240-hour postdose blood draws and for additional clinical procedures.</td></tr>
<tr><td>Safety Assessments</td><td>All safety assessments, including adverse events, clinical laboratory evaluations, vital sign measurements, ECG results, and physical examination findings are presented in the data listings and summarized using descriptive statistics, if appropriate. Abnormal laboratory values (i.e.,</td></tr>
</table>

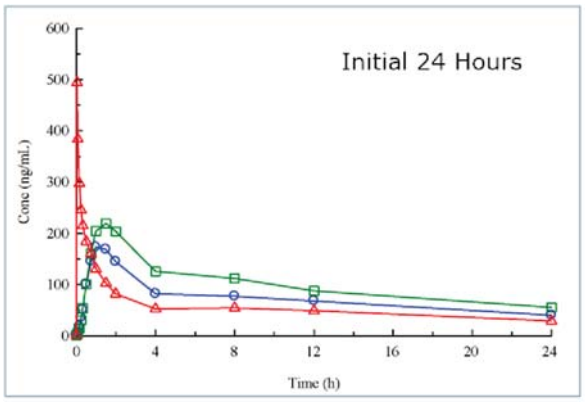
	outside normal range) for hematology, chemistry, and urinalysis tests were summarized.
Statistical Methods	Comparison of the PK parameters Cmax, AUC0-t, and AUC0-inf for diazepam between each test formulation (suspension and solution) and the reference (IV) formulation was done using an analysis of variance statistical model with sequence, subject within sequence, treatment, and period as the classification variables. Parameters were natural log-transformed and those for the 5 mg IV were normalized to 10 mg before analysis. Confidence intervals (90%) were constructed for the geometric mean treatment ratios, each test to each reference, of the three parameters using the log-transformed data and the two one-sided t-tests procedure. The point estimates and confidence limits were exponentiated back to the original scale.

RESULTS:

Following figure represents mean plasma concentration versus time profiles of diazepam, sorted by treatment on linear scale.

Arithmetic Mean Plasma Diazepam Concentrations (Initial 24 Hours)—Linear Axis





Following tables represents diazepam pharmacokinetic parameters following administration of diazepam nasal spray and injection formulations

	Diazepam Nasal Spray (10 mg/100µL)				Diazepam Injection	
	NRL-1.A Suspension		NRL-1.B Solution		5 mg/mL IV	
Parameter [a]	n	Mean (SD) [b]	n	Mean (SD) [b]	n	Mean (SD) [b]
C_{max} (ng/mL)	24	221 (78.6)	24	272 (100)	24	555 (316)
T_{max} (h)	24	1.00 (0.6, 2.0)	24	1.50 (0.8, 4.0)	24	0.03 (0.03, 0.50)
AUC_{0-t} (h×ng/mL)	24	5229 (1463)	24	7340 (1882)	24	3832 (1150)
$AUC_{0-\infty}$ (h×ng/mL)	20	5381 (1409)	20	7338 (2072)	24	4104 (1318)
λz (h^{-1})	20	0.0142 (0.0053)	20	0.0155 (0.0046)	24	0.0142 (0.0055)
$t_{½}$ (h)	20	56.2 (23.0)	20	49.2 (16.9)	24	56.2 (21.0)

a: Mean values are presented as arithmetic means.
b: Median (min, max) reported for T_{max}

Note: The non-aqueous solution (NRL-1.B) was the final formulation developed for the NDA.

CONCLUSIONS:

- Diazepam was extensively absorbed after intranasal administration of non-aqueous solution (NRL-1.B) with an absolute bioavailability of 97%. The absolute bioavailability 67% from an aqueous suspension (NRL-1.A) and with an with a median Tmax of 1.5 hours and 1 hour respectively.
- The mean elimination t½ of diazepam was comparable across all treatment groups (intranasal or IV).

DIAZ.001.02: Pharmacokinetics, Dose Proportionality, and Comparison of One and Two Doses of Diazepam after Administration of NRL-1 to Healthy Volunteers

Objectives:

Primary Objective:

• To assess the pharmacokinetics and dose proportionality of diazepam after single intranasal doses of NRL-1 to healthy volunteers under fasted conditions.

Secondary Objectives:

• To compare the pharmacokinetic parameters of diazepam after one and two dose treatments of NRL-1;

• To assess the safety and tolerability of diazepam after intranasal administration.

<table>
<tr><td>Study Design</td><td>This study was a Phase 1, open-label, randomized, three single dose, three-period, six-sequence crossover study, followed by a fourth two-dose period, that consisted of a screening period, baseline period, and an open-label treatment period.
Screening Period: Subjects underwent screening within 21 days prior to entering into the open-label treatment phase of the study.
Open-Label Treatment Period: Thirty-six (36) eligible subjects were randomized, after an overnight fast, into one of six sequences to receive single doses of 5, 10, and 20 mg of NRL-1 in the first three treatment periods (Treatments 1, 2, and 3) followed by two 10 mg doses of NRL-1 4 hours apart (Treatment 4).</td></tr>
<tr><td>Study Population</td><td>Healthy Subjects (males and female)
Age: 18-55 years
Body Weight: 51 kg to 111kg
36 subjects were enrolled and 29 completed the study</td></tr>
<tr><td>Treatments</td><td>Subjects were randomized, after an overnight fast, into one of six sequences to receive single doses of 5, 10, and 20 mg of NRL-1 in the first three treatment periods (Treatments 1, 2, and 3) followed by two 10 mg doses of NRL-1 4 hours apart (Treatment 4).</td></tr>
<tr><td>Analysis</td><td>A validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of plasma diazepam and its active metabolite nordiazepam concentrations. Diazepam-d5 and nordiazepam-d5 were used as the internal standards. The lower limit of quantitation was 1 ng/mL and 100 pg/mL respectively for both analytes. Following table describes the summary of method validation and performance. Summary of control results are presented in the table below.

Diazepam
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>3.0, 50, 500 and 750 ng/mL</td><td>1.0, 2.0, 20, 100, 200, 400, 800 and 1000 ng/mL</td></tr>
</table>
</td></tr>
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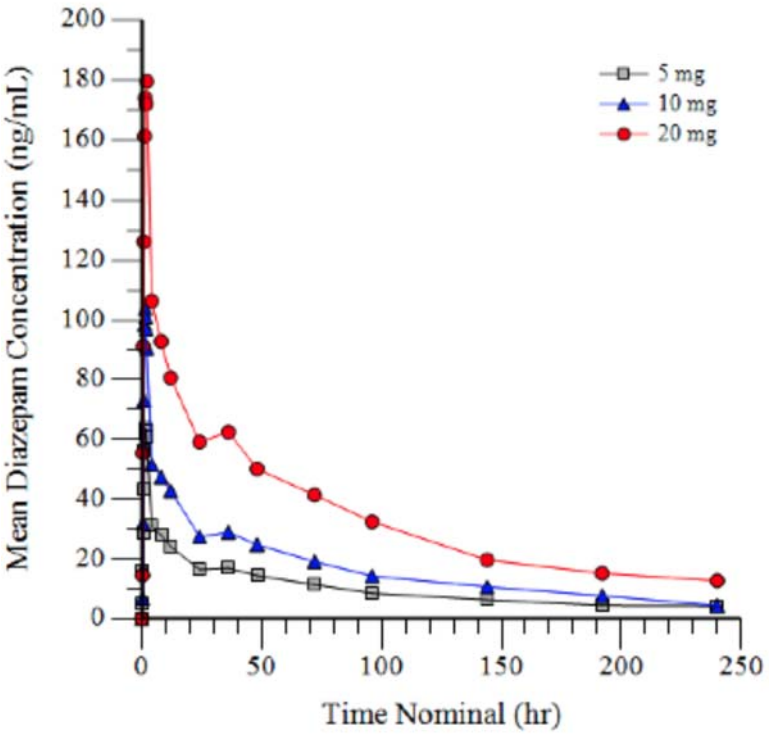
<table>
<tr><td></td><td>
<table>
<tr><td>Between Batch Precision (%CV)</td><td>3.55 to 6.04</td><td>2.20 to 5.00</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-5.29 to -0.67</td><td>-4.62 to 4.67</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.9976</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">1 to 1000 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">1 ng/mL</td></tr>
</table>
</td></tr>
<tr><td>Pharmacokinetic Assessments</td><td>The following pharmacokinetic parameters for diazepam and desmethyldiazepam were calculated using non-compartmental analysis: maximum plasma concentration (Cmax), time to Cmax (tmax), area under the curve to the final time with a concentration equal to or greater than the lower limit of quantitation [AUC(0-t)] and to infinity [AUC(inf)], elimination rate constant (λz), and half-life (t½), and, for diazepam only, clearance (CL/F) and volume of distribution (Vz/F) uncorrected for bioavailability (F). For the two-dose treatment, a Cmax and tmax for each dose was calculated; the AUCs were calculated for the complete treatment period.
Blood samples for the measurement of plasma concentrations of diazepam and desmethyldiazepam were collected as follows: Single-dose treatment periods (Treatments 1, 2, and 3): Before (0, pre-dose) and at 10, 20, 30, and 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 4, 8, 12, 24, 36, 48, 72, 96, 144, 192, and 240 hours after dosing. Two-dose treatment period (Treatment 4): Before (0, pre-dose) and at 10, 20, 30, and 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 4*, 4.167, 4.33, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 8, 12, 24, 36, 48, 72, 96, 144, 192, and 240 hours after the first dose (*The blood sample was collected immediately prior to administration of the second dose). Actual blood collection times can vary as follows: 1) ± 2 minutes for the 10 to 60 minute samples, 2) ± 5 minutes for the 1.25 to 8 hour samples, 3) ± 15 minutes for the 12 and 24 hour samples, and 4) ± 2 hours for the 36 to 240 hour samples. Actual blood sampling times were used for all pharmacokinetic analyses.</td></tr>
<tr><td>Safety Assessments</td><td>All safety assessments, including adverse events, clinical laboratory evaluations, vital sign measurements, ECG results, and physical examination findings are presented in the data listings and summarized using descriptive statistics, if appropriate. Abnormal laboratory values (i.e., outside normal range) for hematology, chemistry, and urinalysis tests were summarized.</td></tr>
<tr><td>Statistical Methods</td><td>Individual subject plasma concentrations, actual sampling times, and pharmacokinetic parameters will be listed by analyte and treatment. Descriptive statistics will be calculated by analyte and treatment for plasma concentrations and pharmacokinetic parameters. Individual subject and mean plasma concentrations will be displayed on linear and semi-logarithmic axes.</td></tr>
</table>

	The pharmacokinetic parameters Cmax, AUC(0-t), and AUC(inf) for diazepam and desmethyldiazepam will be compared among treatments using an analysis of variance (ANOVA) model with treatment, period, sequence, and subject within sequence as the classification variables using the natural logarithms of the data. Confidence intervals (90%) will be constructed for the geometric mean ratios, NRL-1-to-Diastat and NRL-1-to-oral diazepam, of the three parameters using the log-transformed data and the two one-sided t-tests procedure. The point estimates and confidence limits will be exponentiated back to the original scale. Comparability between NRL-1 and Diastat and NRL-1 and oral diazepam will be assessed from the geometric mean ratios and 90%.

RESULTS:

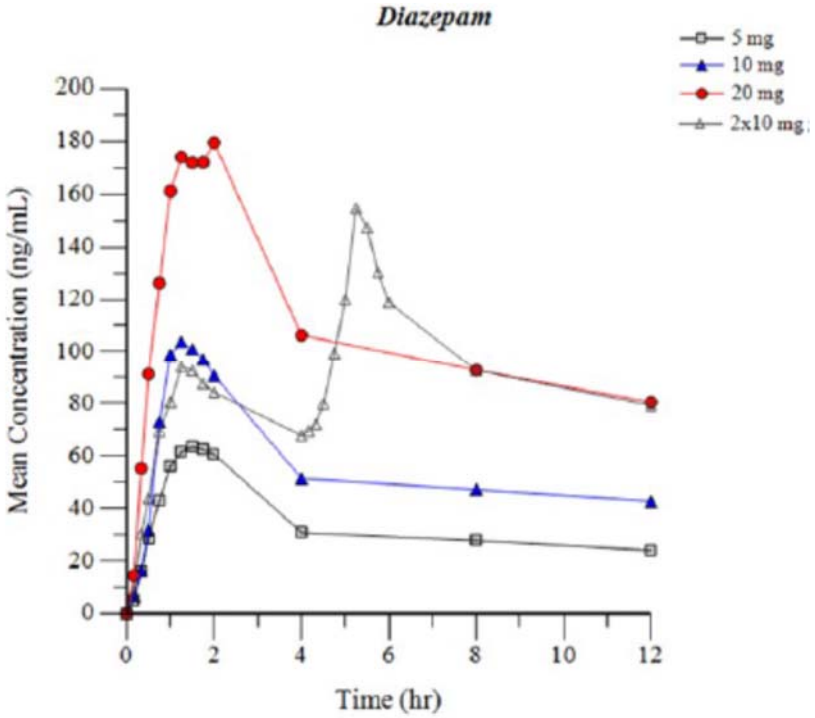
Following figure represents mean plasma concentration versus time profiles of diazepam, sorted by treatment on linear scale.

Mean Plasma Concentration-Time Profiles of Diazepam (Single Dose) Sorted by Dose: Linear Scale

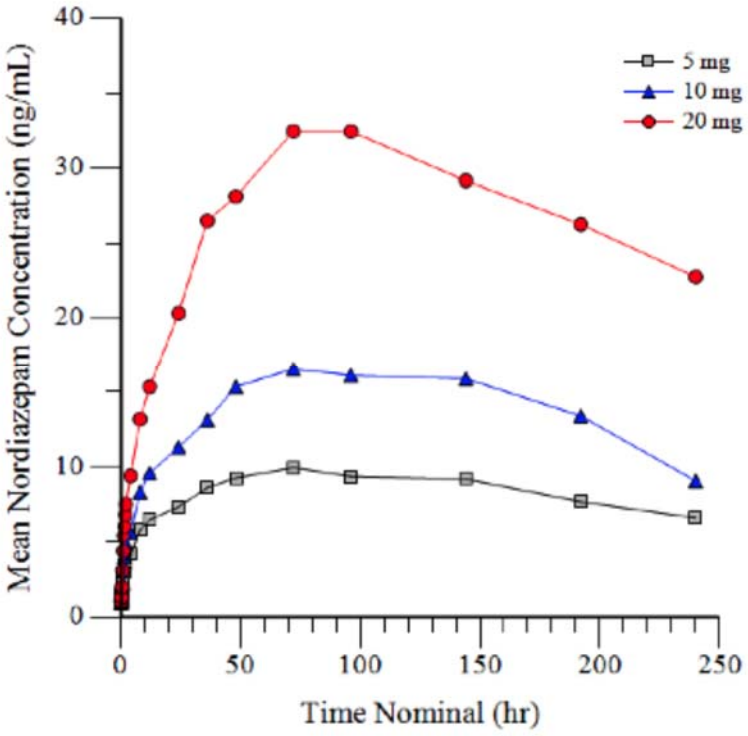


NRL-1 Diazepam

Diazepam Plasma Concentration versus Time Curves Initial Part



Mean Plasma Concentration-Time Profiles of Nordiazepam (Single Dose) Sorted by Dose



Following tables represents diazepam pharmacokinetic parameters following administration of diazepam nasal spray 5 mg, 10 mg and 20 mg

Statistic	C_{max} (ng/mL)	t_{max} (hr)	t_{lag} (hr)	AUC_{0-t} (hr•ng/mL)	$AUC_{0-\infty}$ (hr•ng/mL)	AUC_{Extrap} (%)	λ_z (1/hr)	$t_{1/2}$ (hr)	Cl/F (L/hr)	V_zF (L)
N	32	32	32	32	25	25	25	25	25	25
Mean	85.59	–	–	2232	2411	15	0.0119	70	2.83	308
SD	57.48	–	–	1144	1164	9	0.00548	30	2.05	298
CV%	67	–	–	51	48	64	46	42	72	97
Min	4.89	0.33	0	377	500	1	0.00569	27	0.96	56
Median	69.11	1.5	0	2052	2182	14	0.011	63	2.29	188
Max	219.84	8	0.17	4502	5225	37	0.03	122	10.01	1084
Geo Mean	64.2	–	–	1910	2110	11	0.0108	64	2.37	220
CV% Geo Mean	106	–	–	68	62	99	47	47	62	93

Abbreviations: – = not calculable, CV = coefficient of variation, Geo = geometric, Max = maximum, Min = minimum.
Source: Appendix 16.1.13, Pharmacokinetic Report, Table 9

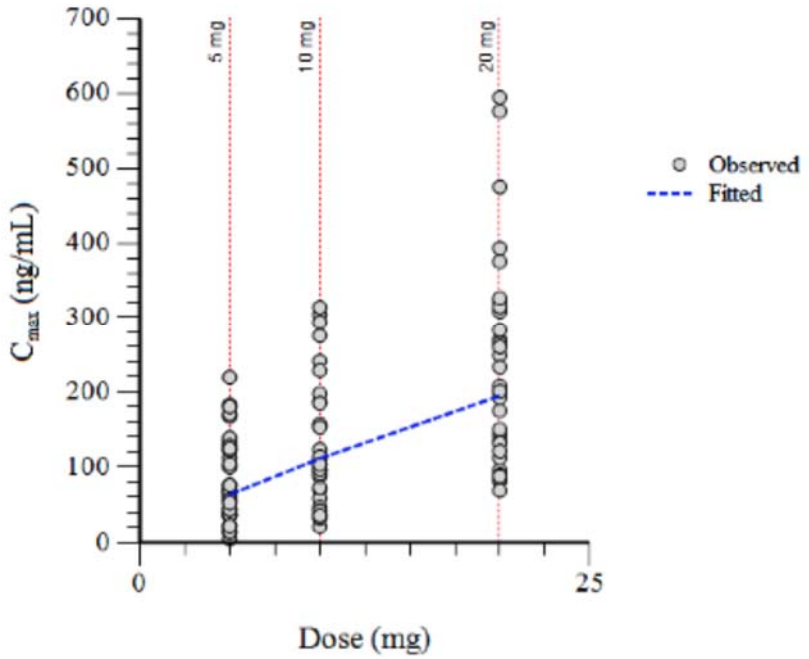
Statistic	C_{max} (ng/mL)	t_{max} (hr)	t_{lag} (hr)	AUC_{0-t} (hr•ng/mL)	$AUC_{0-\infty}$ (hr•ng/mL)	AUC_{Extrap} (%)	λ_z (1/hr)	$t_{1/2}$ (hr)	Cl/F (L/hr)	V_zF (L)
N	31	31	31	31	27	27	27	27	27	27
Mean	133.58	–	–	3803	4505	12	0.0118	71	3.12	333
SD	85.7	–	–	1990	2528	10	0.00552	32	2.16	318
CV%	64	–	–	52	56	79	47	44	69	95
Min	22.02	0.75	0	835	1083	2	0.0049	26	0.81	76
Median	104.3	1.5	0	3485	4301	9	0.0112	62	2.33	218
Max	314.12	36	0.17	9002	12347	33	0.03	141	9.23	1332
Geo Mean	106.95	–	–	3303	3854	9	0.0107	65	2.59	242
CV% Geo Mean	82	–	–	62	65	110	48	48	65	91

Abbreviations: – = not calculable, CV = coefficient of variation, Geo = geometric, Max = maximum, Min = minimum.
Source: Appendix 16.1.13, Pharmacokinetic Report, Table 10

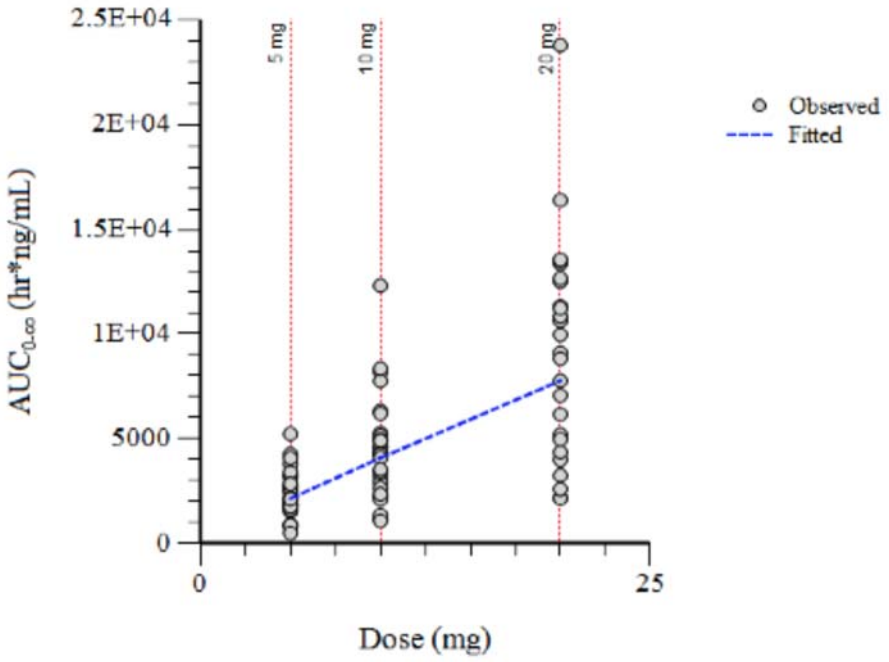
Statistic	C_{max} (ng/mL)	t_{max} (hr)	t_{lag} (hr)	AUC_{0-t} (hr•ng/mL)	$AUC_{0-\infty}$ (hr•ng/mL)	AUC_{Extrap} (%)	λ_z (1/hr)	$t_{1/2}$ (hr)	Cl/F (L/hr)	V_zF (L)
N	32	32	32	32	26	26	26	26	26	26
Mean	235.28	–	–	7946	9168	12	0.0115	74	3.22	304
SD	137.94	–	–	4104	5055	11	0.00516	36	2.41	207
CV%	59	–	–	52	55	91	45	49	75	68
Min	68.98	0.5	0	1934	2158	1	0.00393	33	0.84	69
Median	204.9	1.38	0	7794	9527	8	0.0104	66	2.1	247
Max	594.72	8	0	19024	23775	40	0.02	176	9.27	1039
Geo Mean	199.57	–	–	6864	7711	8	0.0104	66	2.59	249
CV% Geo Mean	65	–	–	63	72	152	49	49	72	73

Abbreviations: – = not calculable, CV = coefficient of variation, Geo = geometric, Max = maximum, Min = minimum.
Source: Appendix 16.1.13, Pharmacokinetic Report, Table 11

Plot of Diazepam Cmax versus Dose (Single Dose)



Plot of Diazepam AUC0–∞ versus Dose (Single Dose)



Analysis of Diazepam Dose Proportionality: Cmax and AUC0–∞ (Single Dose)

Effect Level	Dependent	Estimate	Lower CI	Upper CI
Slope	C_{max}	0.81	0.62	1.00
Slope	$AUC_{0-\infty}$	0.93	0.80	1.06

Abbreviations: CI = confidence interval.
Source: Appendix 16.1.13, Pharmacokinetic Report, Table 15

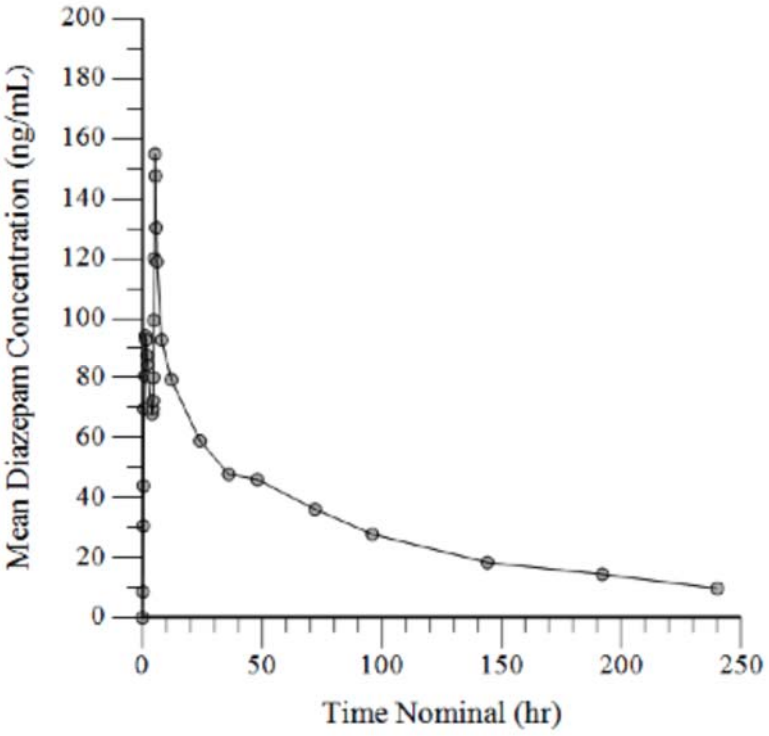
Analysis of Nordiazepam Dose Proportionality: Cmax and AUC0–∞ (Single Dose)

Effect Level	Dependent	Estimate	Lower CI	Upper CI
Slope	C_{max}	0.79	0.67	0.90
Slope	AUC_{0-t}	0.83	0.71	0.95
Slope	$AUC_{0-\infty}$	0.55	0.31	0.79

Abbreviations: CI = confidence interval
Source: Appendix 16.1.13, Pharmacokinetic Report, Table 16

Note: The power model was used to test dose proportionality for single doses of NRL-1 at the 5, 10, and 20 mg dose levels. Systemic exposure of diazepam and nordiazepam increased with increasing doses, the 90% CI for β (slope) were outside 80 to 125% for both Cmax and AUC0-∞. However, the PK parameters Cmax and AUC0-∞ were essentially dose proportional.

Mean Plasma Concentration-Time Profiles of Diazepam (Multiple Dose)



Summary Statistics of Diazepam Pharmacokinetic Parameters (Multiple Dose)

Statistic	R_{cmax}	R_{AUC}	$C_{max(0-4}$ (ng/mL)	$C_{max(4-8}$ (ng/mL)	AUC_{0-4} (hr*ng/mL)	AUC_{4-8} (hr*ng/mL)	C_{max} (ng/mL)	t_{max} (hr)	t_{lag} (hr)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	AUC_{Extrap} (%)	λ_z (1/hr)	$t_{1/2}$ (hr)	Cl/F (L/hr)	V_z/F (L)
N	29	29	29	29	29	29	29	29	29	29	25	25	25	25	25	25
Mean	1.61	1.81	122.98	161.41	282	433	180.18	–	–	7297	7936	12	0.0115	74	3.41	366
SD	1.36	1.31	90.04	124.58	201	302	122.14	–	–	4236	4535	10	0.00552	33	2.02	284
CV%	84	72	73	77	71	70	68	–	–	58	57	84	48	45	59	78
Min	0.23	0.51	13.65	24.17	42	70	27.63	0.5	0	1165	2229	1	0.00492	29	1.02	87
Median	1.39	1.63	99.22	138.38	233	403	168.67	5.25	0	6561	6338	10	0.0103	67	3.16	240
Max	7.23	7.67	344.7	475.39	728	1096	475.39	12	0.17	15940	19689	34	0.02	141	8.97	1100
Geo Mean	1.25	1.54	91.52	114.55	212	327	137.16	–	–	6067	6831	8	0.0104	67	2.93	283
CV% Geo Mean	84	60	100	113	98	97	97	–	–	73	61	149	50	50	61	84

Abbreviations: – = not calculable, CV = coefficient of variation, Geo = geometric, Max = maximum, Min = minimum, R_{AUC} = Ratio of $AUC_{max(4-8)}/AUC_{max(0-4)}$, R_{cmax} = Ratio of $C_{max(4-8)}/C_{max(0-4)}$.
Source: Appendix 16.1.13, Pharmacokinetic Report, Table 21

CONCLUSIONS:
Diazepam and nordiazepam exposure increased essentially proportionally with increasing diazepam nasal spray dose of 5 mg, 10 mg and 20 mg

DIAZ.001.03: A Three-Period, Three-Treatment, Six-Sequence Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Diazepam After Administration of NRL-1, Diastat®, and Oral Valium to Healthy Volunteers (DIAZ.001.03)

Objectives:

Primary objective:

• To assess the comparative bioavailability of diazepam after intranasal administration as NRL-1 and rectal administration as Diastat (diazepam rectal gel) in healthy volunteers under fasted conditions.

Secondary objectives:

• To assess the comparative bioavailability of diazepam after intranasal administration as NRL-1 and oral administration as Valium (diazepam oral tablets) in healthy volunteers under fasted conditions.

• To evaluate the safety of NRL-1 in healthy volunteers.

Study Design	This study was a Phase 1, open-label, randomized, single-dose, three-treatment, three-period, six-sequence crossover study that consisted of a screening period, baseline period, and an open-label treatment period. Screening Period: Subjects underwent screening within 21 days prior to entering into the open-label treatment phase of the study. Open-Label Treatment Period: Forty-eight (48) eligible subjects were randomized after an overnight fast into one of six sequences that received a single dose of NRL-1, Diastat (diazepam rectal gel), or oral Valium (diazepam tablets) in three treatment periods (Treatment period 1, 2, and 3). Dosing in the Valium (diazepam tablets) arm was 10 mg as an internal reference. NRL-1 and Diastat were dosed by weight categories with subjects 51 to 75 kg of weight receiving 15 mg of diazepam and 76 to 111 kg of weight receiving 20 mg of diazepam. Blood samples were collected for 240 hours after dosing. Treatments were separated by a minimum 28-day wash out period.
Study Population	Healthy Subjects (males and female) Age: 18-55 years Body Weight: 51 to 111 kg 48 subjects were enrolled and 45 completed the study
Treatments	NRL-1, Diastat (diazepam rectal gel), or oral Valium

<table>
<tr><td>Analysis</td><td>A validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of plasma diazepam and its active metabolite nordiazepam concentrations. Diazepam-d5 and nordiazepam-d5 were used as the internal standards. The lower limit of quantitation was 1 ng/mL and 100 pg/mL respectively for both analytes. Following table describes the summary of method validation and performance. Summary of control results are presented in the table below.

Diazepam
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>3.0, 50, 500 and 750 ng/mL</td><td>1.0, 2.0, 20, 100, 200, 400, 800 and 1000 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>3.95 to 3.96</td><td>3.08 to 4.96</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-1.82 to 7.33</td><td>-4.30 to 4.06</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.9984</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">1 to 1000 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">1 ng/mL</td></tr>
</table></td></tr>
<tr><td>Pharmacokinetic Assessments</td><td>The following pharmacokinetic parameters for diazepam and desmethyl-diazepam were calculated using non-compartmental analysis: Cmax, time to Cmax (tmax), area under the curve to the final time with a concentration equal to or greater than the lower limit of quantitation [AUC(0-t)] and to infinity [AUC(inf)], elimination rate constant (λz) and half-life (t½), and, for diazepam only, clearance (CL/F) and volume of distribution (Vz/F) uncorrected for bioavailability (F).
Blood samples for the measurement of plasma concentrations of diazepam and desmethyl-diazepam were collected before (0, pre-dose) and 10, 20, 30, and 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 4, 8, 12, 24, 36, 48, 72, 96, 144, 192, and 240 hours after dosing. Actual blood collection times were allowed to vary as follows: 1) ± 2 minutes for the 10 to 60 minute samples, 2) ± 5 minutes for the 1.25 to 8 hour samples, 3) ± 15 minutes for the 12 and 24 hour samples, and 4) ± 2 hours for the 36 to 240 hour samples.</td></tr>
<tr><td>Safety Assessments</td><td>Adverse events were collected and reviewed to evaluate the safety and tolerability of diazepam nasal solution. Other safety measures included physical examination, vital sign measurement, ECGs, and clinical laboratory tests.</td></tr>
</table>

Statistical Methods	Individual subject plasma concentrations, actual sampling times, and pharmacokinetic parameters were listed by analyte and treatment. Descriptive statistics were calculated by analyte and treatment for plasma concentrations and pharmacokinetic parameters. Individual subject and mean plasma concentrations were displayed on linear and semi-logarithmic axes. The pharmacokinetic parameters Cmax, AUC(0-t), and AUC(inf) for diazepam and desmethyldiazepam were compared among treatments using an analysis of variance (ANOVA) model with treatment, period, sequence, and subject within sequence as the classification variables using the natural logarithms of the data. Confidence intervals (90%) will be constructed for the geometric mean ratios, NRL-1-to-Diastat and NRL-1-to-oral Valium, of the three parameters using the log-transformed data and the two one-sided t-tests procedure. The point estimates and confidence limits were exponentiated back to the original scale. Comparability between NRL-1 and Diastat and NRL-1 and oral Valium was assessed from the geometric mean ratios and 90% confidence intervals for the three parameters.

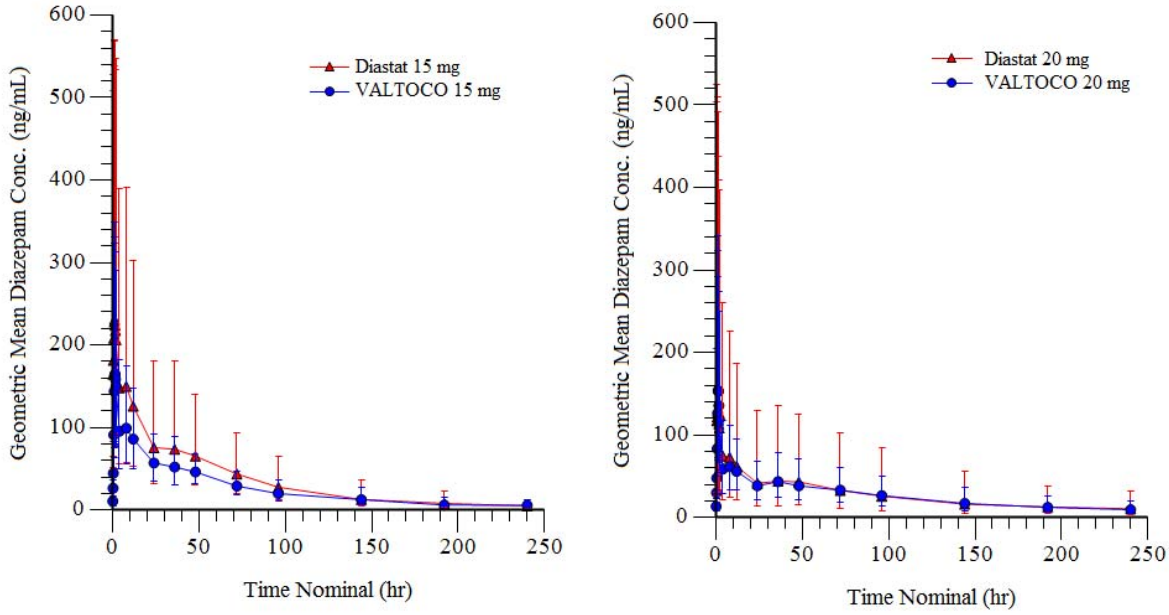
A total of 48 healthy volunteer subjects were enrolled and 46 received at least 1 dose of NRL-1.

RESULTS:

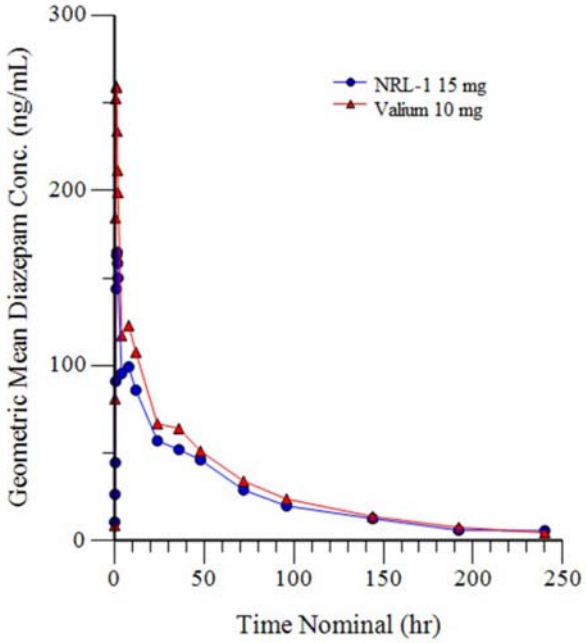
A total of 48 healthy volunteer subjects were enrolled and 46 received at least 1 dose of NRL-1. A total of 20 subjects with a body weight of 51 to 75 kg and a total of 28 subjects had a body weight of 76 to 111 kg were included in the safety analysis data set. Forty-four (44) subjects completed the study.

Following figure represents mean plasma diazepam concentration-time profiles per treatment group on linear scale.

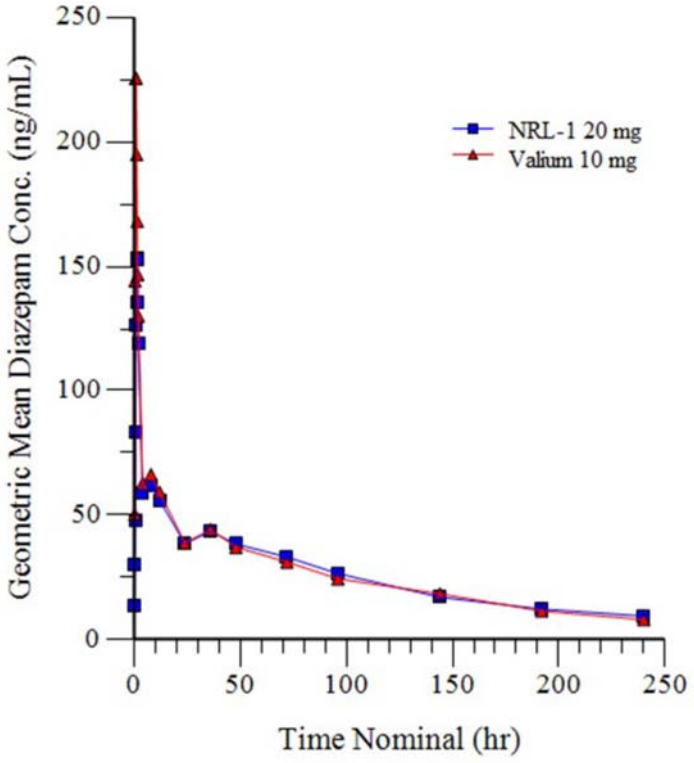
Mean Plasma Concentration-Time Profiles of Diazepam, 15 and 20 mg VALTOCO Nasal Spray and 15 and 20 mg Diazepam Rectal Gel (Geometric Mean with Upper and Lower 1 Geometric Deviation)



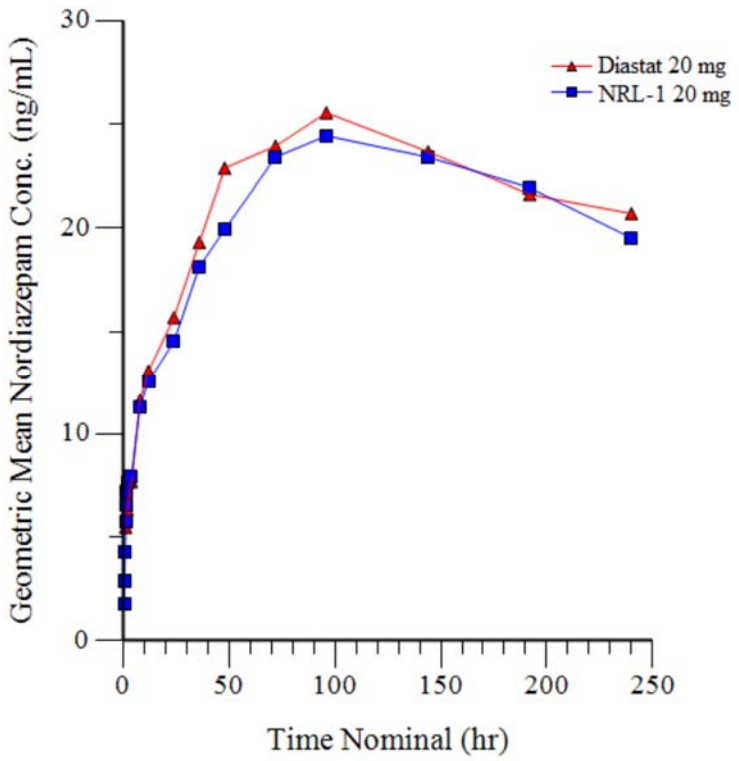
Mean Plasma Concentration-Time Profiles of Diazepam, 15 mg NRL-1 and 10 mg Valium (Geometric Mean): Linear Scale



Mean Plasma Concentration-Time Profiles of Diazepam, 20 mg NRL-1 and 10 mg Valium (Geometric Mean): Linear Scale



Mean Plasma Concentration-Time Profiles of Nordiazepam, 20 mg NRL-1 and 20 mg Diastat (Geometric Mean): Linear Scale



Following tables represents diazepam pharmacokinetic parameters for 15 mg and 20 mg Diastat.

Summary Statistics of Diazepam Pharmacokinetic Parameters, 15 mg Diastat

Statistic	C_{max} (ng/mL)	t_{max} (hr)	t_{lag} (hr)	AUC_{0-t} (hr*ng/ mL)	$AUC_{0-\infty}$ (hr*ng/ mL)	AUC_{extr} (%)	λ_z (1/hr)	Half-life (hr)	Cl/F (L/hr)	V_z/F (L)	C_{max}/D (ng/mL/mg)	$AUC_{0-\infty}/D$ (hr*ng/mL/mg)
N	17	17	17	17	17	17	17	17	17	17	17	17
Mean	333.46	1.9	0.01	10649	11583	8	0.0147	62	2.38	249	22	772
SD	110.93	2.35	0.04	4478	4838	9	0.00676	40	4.25	593	7.4	323
CV%	33	124	412	42	42	115	46	64	179	238	33	42
Min	10.28	0.33	0	646	798	1	0.0037	26	0.7	43	0.69	53
Median	361.54	1.25	0	10717	10968	3	0.0151	46	1.37	88	24.1	731
Max	457.21	8	0.17	20799	21305	34	0.03	187	18.8	2541	30.48	1420
Geo Mean	280.28	1.19	NA	9092	9953	4	0.013	53	1.51	116	18.69	664
CV% Geo Mean	109	117	NA	87	83	208	58	58	83	114	109	83

Abbreviations: – = not calculable, CV = coefficient of variation, Geo = geometric, Max = maximum, Min = minimum, N = number

Summary Statistics of Diazepam Pharmacokinetic Parameters, 20 mg Diastat

Statistic	C_{max} (ng/mL)	t_{max} (hr)	t_{lag} (hr)	AUC_{0-t} (hr*ng/ mL)	$AUC_{0-\infty}$ (hr*ng/ mL)	AUC_{extr} (%)	λ_z (1/hr)	Half-life (hr)	Cl/F (L/hr)	V_z/F (L)	C_{max}/D (ng/mL/mg)	$AUC_{0-\infty}/D$ (hr*ng/mL/mg)
N	27	27	27	27	27	27	27	27	27	27	27	27
Mean	258.39	1.04	0.02	9675	12281	17	0.00889	93	5.77	780	13	614
SD	159.61	0.78	0.07	6296	9696	11	0.00359	41	9.24	1559	7.98	485
CV%	62	75	380	65	79	66	40	45	160	200	62	79
Min	5.57	0.17	0	458	591	2	0.00363	43	0.53	115	0.28	30
Median	239.25	1	0	10133	10943	15	0.00791	88	1.83	187	11.96	547
Max	657.18	4	0.33	23571	37622	39	0.02	191	33.85	7344	32.86	1881
Geo Mean	163.63	0.79	NA	6424	7855	13	0.00819	85	2.55	311	8.18	393
CV% Geo Mean	229	92	NA	172	170	95	44	44	170	163	229	170

Abbreviations: – = not calculable, CV = coefficient of variation, Geo = geometric, Max = maximum, Min = minimum, N = number

Summary Statistics of Diazepam Pharmacokinetic Parameters, 15 mg NRL-1

Statistic	C_{max} (ng/mL)	t_{max} (hr)	t_{lag} (hr)	AUC_{0-t} (hr*ng/ mL)	$AUC_{0-\infty}$ (hr*ng/ mL)	AUC_{extr} (%)	λ_z (1/hr)	Half-life (hr)	Cl/F (L/hr)	V_z/F (L)	C_{max}/D (ng/mL/mg)	$AUC_{0-\infty}/D$ (hr*ng/mL/mg)
N	17	17	17	17	17	17	17	17	17	17	17	17
Mean	264.64	1.48	0	7098	7638	6	0.0149	54	2.31	174	18	509
SD	175.07	0.79	0	3065	3506	6	0.006	22	0.84	89	11.67	234
CV%	66	53	NA	43	46	94	40	41	36	51	66	46
Min	90.03	0.75	0	3622	3907	1	0.00646	25	1.04	48	6	260
Median	200.99	1.25	0	5664	5715	4	0.0124	56	2.62	148	13.4	381
Max	781.92	4	0	12699	14397	21	0.03	107	3.84	411	52.13	960
Geo Mean	225.66	1.33	NA	6552	6999	4	0.0138	50	2.14	156	15.04	467
CV% Geo Mean	60	47	NA	42	44	116	42	42	44	52	60	44

Abbreviations: – = not calculable, CV = coefficient of variation, Geo = geometric, Max = maximum, Min = minimum, N = number

Summary Statistics of Diazepam Pharmacokinetic Parameters, 20 mg NRL-1

Statistic	C_{max} (ng/mL)	t_{max} (hr)	t_{lag} (hr)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	AUC_{extr} (%)	λ_z (1/hr)	Half-life (hr)	Cl/F (L/hr)	V_z/F (L)	C_{max}/D (ng/mL/mg)	$AUC_{0-\infty}/D$ (hr*ng/mL/mg)
N	28	28	28	28	28	28	28	28	28	28	28	28
Mean	227.23	1.75	0	7324	10010	19	0.00815	113	3.35	400	11	500
SD	128.57	2.11	0	3773	6946	16	0.00311	105	3.93	315	6.43	347
CV%	57	120	NA	52	69	83	38	93	117	79	57	69
Min	18.19	0.5	0	806	911	3	0.00114	46	0.62	121	0.91	46
Median	205.93	1.25	0	6853	9143	13	0.00837	83	2.19	351	10.3	457
Max	494.6	12	0	19784	32503	73	0.02	606	21.96	1800	24.73	1625
Geo Mean	185.53	1.37	NA	6351	8069	15	0.00737	94	2.48	336	9.28	403
CV% Geo Mean	84	63	NA	66	81	82	56	56	81	60	84	81

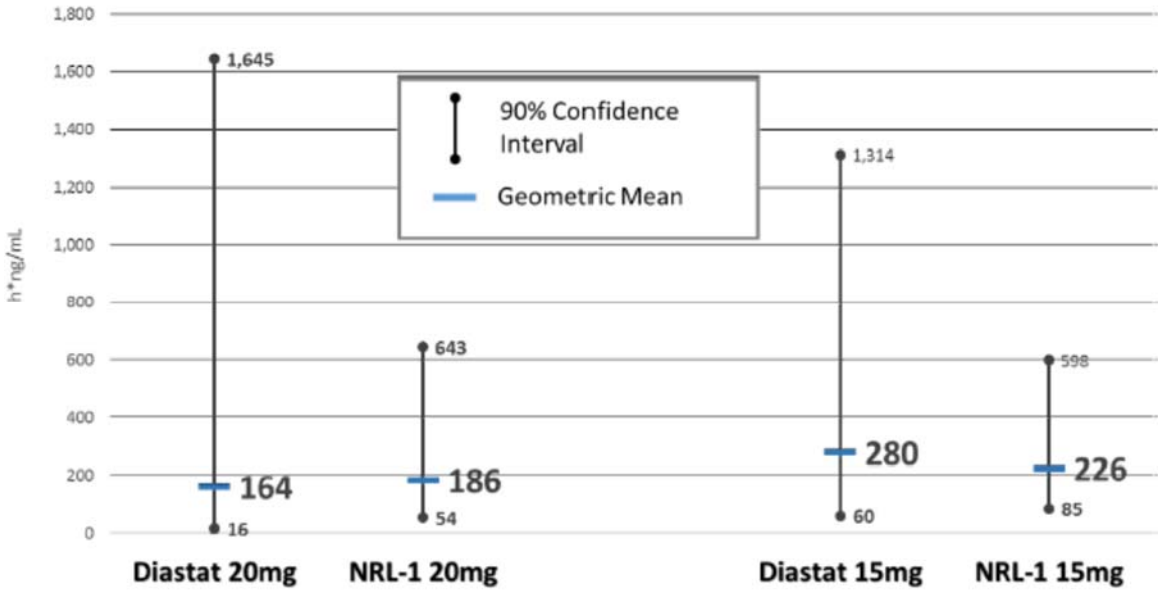
Abbreviations: – = not calculable, CV = coefficient of variation, Geo = geometric, Max = maximum, Min = minimum, N = number

Summary Statistics of Diazepam Pharmacokinetic Parameters, 10 mg Valium

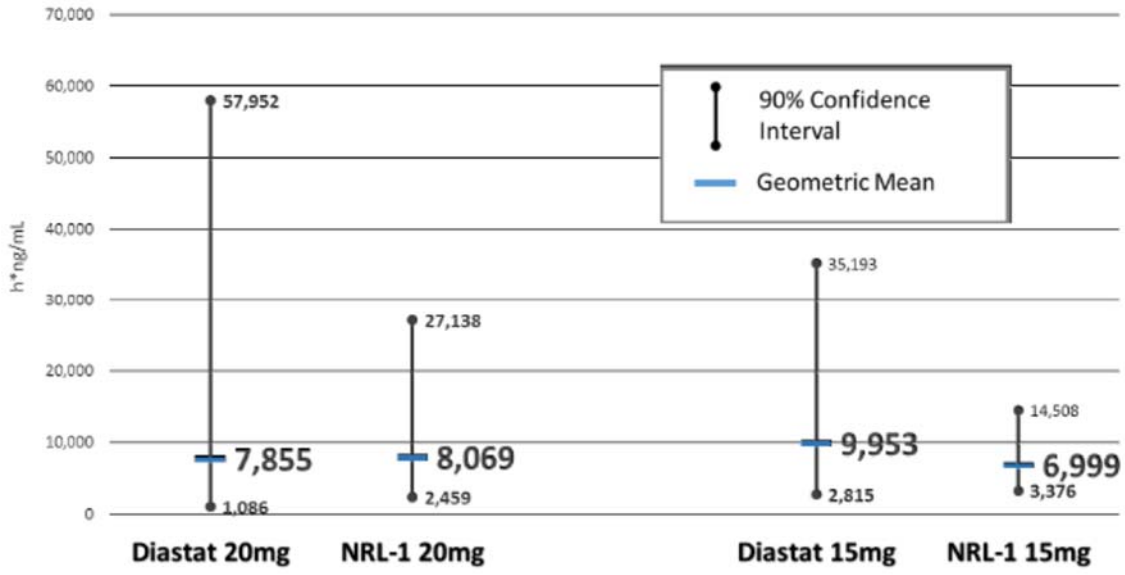
Wt Group	Statistic	C_{max} (ng/mL)	t_{max} (hr)	t_{lag} (hr)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	AUC_{extr} (%)	λ_z (1/hr)	Half-life (hr)	Cl/F (L/hr)	V_z/F (L)	C_{max}/D (ng/mL/mg)	$AUC_{0-\infty}/D$ (hr*ng/mL/mg)
Low	N	17	17	17	17	17	17	17	17	17	17	17	17
	Mean	348.1	1.18	0	8003	8661	7	0.0132	60	1.26	103	35	866
	SD	84.03	0.84	0	2535	2996	5	0.00497	22	0.34	34	8.4	300
	CV%	24	71	NA	32	35	78	38	37	27	33	24	35
	Min	185.23	0.33	NA	5258	5646	1	0.00651	30	0.58	56	18.52	565
	Median	340.79	1	0	7502	7813	6	0.0132	53	1.28	100	34.08	781
	Max	519.53	4	0	14842	17334	19	0.02	107	1.77	193	51.95	1733
	Geo Mean	338.36	1	NA	7693	8268	5	0.0123	56	1.21	98	33.84	827
	CV% Geo Mean	25	63	NA	28	31	122	39	39	31	32	25	31
High	N	28	28	28	28	28	28	28	28	28	28	28	28
	Mean	298.1	0.88	0.01	6784	8379	17	0.00858	95	1.37	177	30	838
	SD	88.09	0.39	0.03	2062	3178	11	0.00344	42	0.57	90	8.81	318
	CV%	30	44	529	30	38	66	40	44	42	51	30	38
	Min	139.47	0.5	0	2489	2781	2	0.00357	43	0.53	92	13.95	278
	Median	279.53	0.75	0	6526	7864	15	0.00857	81	1.27	142	27.95	786
	Max	511.48	2	0.17	10935	18740	47	0.02	194	3.6	445	51.15	1874
	Geo Mean	286.15	0.81	NA	6465	7850	13	0.00792	88	1.27	161	28.62	785
	CV% Geo Mean	30	40	NA	34	38	101	43	43	38	45	30	38

Abbreviations: – = not calculable, CV = coefficient of variation, Geo = geometric, Max = maximum, Min = minimum, N = number

Plots of Diazepam Cmax Versus Treatment/Dose



Plots of Diazepam AUC0–∞ Versus Treatment/Dose



Note: The high-weight subjects showed greater variability compared to the low-weight subjects when diazepam was administered by different routes. Compared to Diastat, intranasal administration of NRL-1 resulted in comparable AUC0-∞ values based on geometric mean values at the 20mg dose but was lower than Diastat at the 15mg dose. This result was apparently due to the more significant impact of body weight and BMI on the exposure of diazepam when administered rectally, which resulted in persons in the 50 kg to 75 kg group given a 15 mg dose having a much higher AUC than those subjects in the greater than 75 kg group who received a 20 mg dose.

A comparison of diazepam Cmax and AUC between 15 mg NRL-1 and 15 mg Diastat is presented in tables below.

Comparison of Diazepam Cmax and AUC between 15 mg NRL-1 and 15 mg Diastat

Wt Group	Dependent	Ratio %Ref	CI 90 Lower	CI 90 Upper
Low	$Ln(C_{max})$	85	57	126
	$Ln(AUC_{0-\infty})$	74	53	102

Abbreviations: CI = confidence interval, Ref = reference, Wt = weight

Comparison of Diazepam Cmax and AUC between 20 mg NRL-1 and 20 mg Diastat

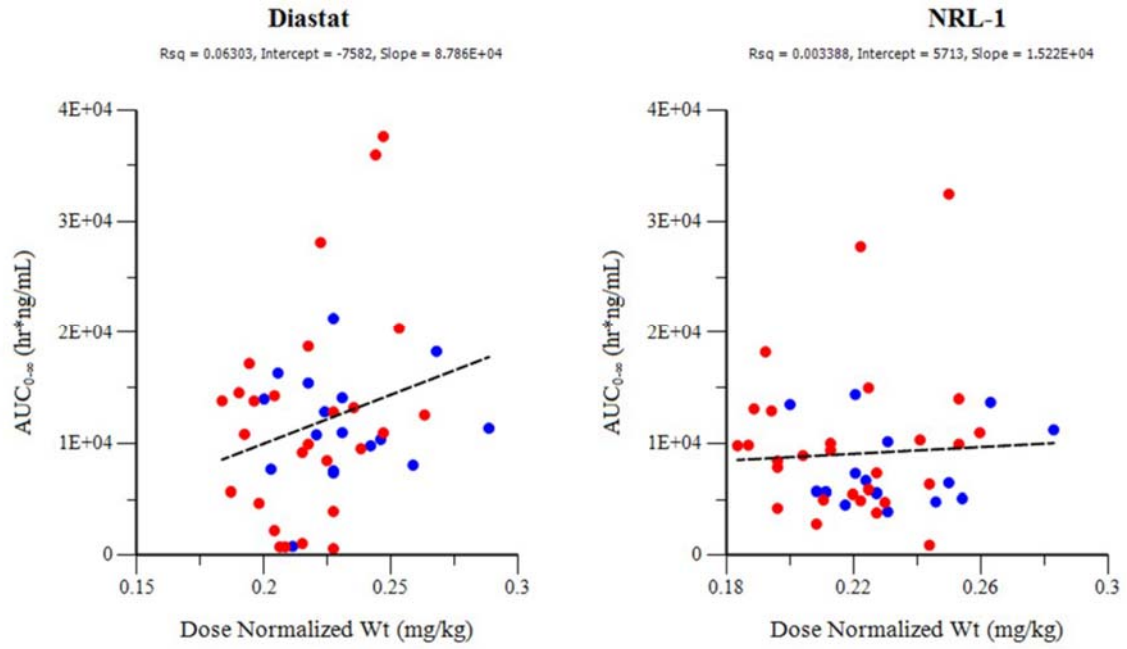
Wt Group	Dependent	Ratio %Ref	CI 90 Lower	CI 90 Upper
High	$Ln(C_{max})$	118	69	202
	$Ln(AUC_{0-\infty})$	100	65	152

Abbreviations: CI = confidence interval, Ref = reference, Wt = weight

Note: Because of high variability in diazepam exposure and body weight-based dosing the Diastat USPI recommends 'acceptable weight ranges for each dose and age category, such that patients will receive between 90% and 180% of the calculated recommended dose'.
The GMR in PK parameters was close to 100% in 20 mg treatment group possibly because of higher number of subjects (n=28) when compared to 15 mg (n=17). The shape of the pharmacokinetic profiles was also similar. Therefore, the efficacy of Valtoco would be expected to be similar to that of rectal gel (Diastat®).

Following figure represents dose normalized weight and AUC distribution for different treatment groups.

AUC0–∞ versus Diazepam Dose-Normalized by Body Weight: Diastat versus NRL-1



A consult was sent to the Office of Study Integrity and Surveillance (OSIS) requesting inspections clinical and analytical sites of pivotal relative bioavailability study DIAZ.001. The OSIS concluded that the data are acceptable based on the records of recent inspections of the study sites.

CONCLUSIONS:

- The comparison of these products show that diazepam PK parameters were less variable for Valtoco (2 to 4-fold lower) and within the range of those seen with Diastat.
- The tmax for NRL-1 was comparable to that of Diastat, but slightly delayed compared to Valium.

- Comparison at both dose levels resulted in 90% CI outside the 80% to 125% range for both PK parameters. Comparison of NRL-1 to Valium indicated a lower dose-normalized Cmax/Dose and AUC0-∞/Dose for both the 15 mg and 20 mg IN dose.
- Variability in Cmax and AUC0-∞ (%CV) geometric mean was lowest with the oral Valium formulation, followed by NRL-1, with Diastat showing the greatest variability.

DIAZ.001.04: An Open-Label, Repeat Dose Pharmacokinetics Study of VALTOCO® (diazepam nasal spray) in Epilepsy Subjects under Seizure and Normal Conditions (DIAZ 001.04)

Objectives:

Primary objective

• To assess the pharmacokinetics (PK) of diazepam after single intranasal doses of VALTOCO® (diazepam nasal spray) administered to Epilepsy subjects during the ictal or peri-ictal period (defined as either during or immediately following a seizure), where the seizure involved motor activity or alteration of awareness. The primary PK variables to determine absorption were the maximum plasma concentration (Cmax) and the area under the curve through 6 hours (AUC(0-6)).

Secondary objective:

• To compare the diazepam Cmax, time to peak concentration (tmax) and AUC(0-6) after single administration of VALTOCO (nasal spray) in Epilepsy subjects during the ictal or periictal period to that after administration of VALTOCO (nasal spray) to the same subjects under normal conditions;

• To compare the diazepam Cmax, tmax, and AUC(0-6) after single administration of VALTOCO (nasal spray) between Epilepsy subjects ages 6 to 11 and those greater than 12 years of age;

• To compare the diazepam Cmax, tmax, and AUC(0-6) after single administration of VALTOCO (nasal spray) in Epilepsy subjects during the ictal or peri-ictal period and that of healthy normal subjects from PK data obtained in the DIAZ.001.02 and DIAZ.001.03 studies;

• To assess the safety and tolerability of diazepam after intranasal administration of VALTOCO (nasal spray).

Study Design	This study was a Phase 1, open-label, PK and safety study in Epilepsy subjects under ictal or peri-ictal (involving motor activity and/or altered awareness) and normal conditions.
Study Population	Epilepsy subjects under ictal or peri-ictal and normal conditions (males and female) Age: seven (7) subjects enrolled were age 6-11, three (3) subjects were age 12-16, and 40 subjects were older than 16. Body Weight: 10 to >76 kg

<table>
<tr><td></td><td>A total of 50 subjects were enrolled with 41 of the subjects completed study.</td></tr>
<tr><td>Treatments</td><td>Two doses of intranasal VALTOCO (nasal spray) were administered at either 5 mg, 10 mg, 15 mg, or 20 mg based on the subject's body weight. The study consisted of a screening period, a baseline period, and a post-dose follow-up period. The VALTOCO (nasal spray) dose was administered during the ictal or peri-ictal period (Treatment 1), and again under normal nonseizing (intra-ictal) conditions (Treatment 2). The dosing was permitted to be done in either order (Treatment 1 or 2 first) with approximately 14-day wash-out between doses.
For Children Age 6-11 Years:
• 10 kg to 18 kg body weight received a 5 mg dose (50 mg/mL, 100 μL) administered as one spray in the left nostril.
• 19 kg to 37 kg received a 10 mg dose (100 mg/mL, 100 μL) administered as one spray in the left nostril.
• 38 kg to 55 kg received a 15 mg dose (75 mg/mL, 100 μL) administered as two 7.5 mg sprays with one in each nostril (the left nostril was sprayed first followed by the right nostril).
• 56 kg to 74 kg received a 20 mg dose (100 mg/mL, 100 μL) of VALTOCO (nasal spray) administered as two 10 mg sprays with one in each nostril (the left nostril was sprayed first followed by the right nostril).
For Age 12 Years or greater:
• 14 kg to 27 kg body weight received a 5 mg dose (50 mg/mL, 100 μL) administered as one spray in the left nostril.
• 28 kg to 50 kg received a 10 mg dose (100 mg/mL, 100 μL) administered as one spray in the left nostril. 51 kg to 75 kg received a 15 mg dose (75 mg/mL, 100 μL) administered as two 7.5 mg sprays with one in each nostril (the left nostril was sprayed first followed by the right nostril).
• Greater than 76 kg received a 20 mg dose (100 mg/mL, 100 μL) of VALTOCO (nasal spray) administered as two 10 mg sprays with one in each nostril (the left nostril was sprayed first followed by the right nostril).</td></tr>
<tr><td>Analysis</td><td>A validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of plasma diazepam and its active metabolite nordiazepam concentrations. Diazepam-d5 and nordiazepam-d5 were used as the internal standards. The lower limit of quantitation was 1 ng/mL and 100 pg/mL respectively for both analytes. Following table describes the summary of method validation and performance. Summary of control results are presented in the table below.

Diazepam
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>3.0, 50, 500 and 750 ng/mL</td><td>1.0, 2.0, 20, 100, 200, 400, 800 and 1000 ng/mL</td></tr>
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<table>
<tr><td></td><td>
<table>
<tr><td>Between Batch Precision (%CV)</td><td>3.55 to 6.04</td><td>2.20 to 5.00</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-5.29 to -0.67</td><td>-4.62 to 4.67</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.9976</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">1 to 1000 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">1 ng/mL</td></tr>
</table>
</td></tr>
<tr><td>Pharmacokinetic Assessments</td><td>The following PK parameters for diazepam were calculated using non-compartmental analysis: Cmax, tmax, AUC(0-6) with a concentration equal to or greater than the lower limit of quantitation.
If a second dose of VALTOCO (nasal spray) was administered due to a subsequent seizure between 4 and 12 hours after the initial dose, when clinically feasible, PK samples were collected based on the time of the second dose at 0 (immediately after the 2nd dose), 30 minutes, and 1, 2, and 4 hours after dosing.
For Treatment 1, the actual time of seizure onset, dose of VALTOCO (nasal spray), time of seizure stop, and time of each blood sample was recorded. PK parameters were determined using actual times of sample collection relative to the administration of VALTOCO (nasal spray).
Blood samples (3 mL) were collected to measure diazepam plasma concentrations following the intranasal administration of VALTOCO (nasal spray). All subjects had samples collected through at least 6 hours after each of the two doses of VALTOCO (nasal spray). Blood samples for PK were obtained at baseline upon admission to the clinical site (EMU or CTRC) for each treatment, and at 15, 30, and 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, and 6 hours after dosing. Blood samples were also obtained, if feasible, at 8 and 12 hours after dosing. If a blood sample collection was delayed, then the collection occurred as soon as feasible and was not skipped even if close to the next blood draw. Actual blood collection times can vary as follows: 1) ± 10 minutes for the 15 to 60 minute samples, 2) ± 15 minutes for the 1.25 to 6-hour samples, and 3) ± 30 minutes for the optional 8 and 12-hour sample.</td></tr>
<tr><td>Safety Assessments</td><td>Data regarding TEAEs was collected during this study. AEs were assessed during the blood sampling period and until follow-up phone calls. All clinically significant abnormal changes from baseline in physical examination findings, vital signs, ECGs, and laboratory evaluations were collected, graded with regards to severity or clinical significance, assessed for causal relationship and recorded on the CRF.</td></tr>
</table>

Statistical Methods	Individual subject plasma concentrations, actual sampling times, and PK parameters were listed by analyte and treatment. Descriptive statistics were calculated by analyte, age group (6 to 11 years being one group and those 12 years of age and over being the other group) and treatment for plasma concentrations and PK parameters. Additional exploratory analyses were conducted to provide descriptive statistics on subjects age 6 to 8 years, 9 to 11 years, 12 to 16 years and over 16 years of age. Individual subject and mean plasma concentrations were displayed on linear and semilogarithmic axes. A separate, but identical, analysis was performed on the observed PK parameters depending on the age group of the subject. The PK parameters Cmax and AUC(0-6) for diazepam were compared for the first dose of VALTOCO (nasal spray) under seizing conditions to the second dose of VALTOCO (nasal spray) under non-seizing conditions using a linear mixed effect model with treatment period if appropriate and clinical site as the classification variables using the natural logarithms of the data. Cmax and AUC(0-6) were normalized to the 10 mg dose prior to analysis. Confidence intervals (CI) (90%) were constructed for the geometric mean ratios (GMR) of the two parameters between the two treatments using the log-transformed data and the two one-sided t-tests procedure. The point estimates and confidence limits were exponentiated back to the original scale. Dose equivalence was concluded if the 90% CI for the GMRs among the two comparisons of the two parameters fell within 80% to 125%. For AUC(0-6) and Cmax, the geometric mean (inverse log-transformed) and the 90% CI for geometric means were compared to those observed in DIAZ.001.02 and DIAZ.001.03 studies. The Cmax and AUC(0-6) determined in epilepsy subjects in the ictal and peri-ictal period were compared between the same subject in a normative state. The Cmax and AUC(0-6) were visually compared between the two age groups in both seizure/non-seizure conditions.

RESULTS:

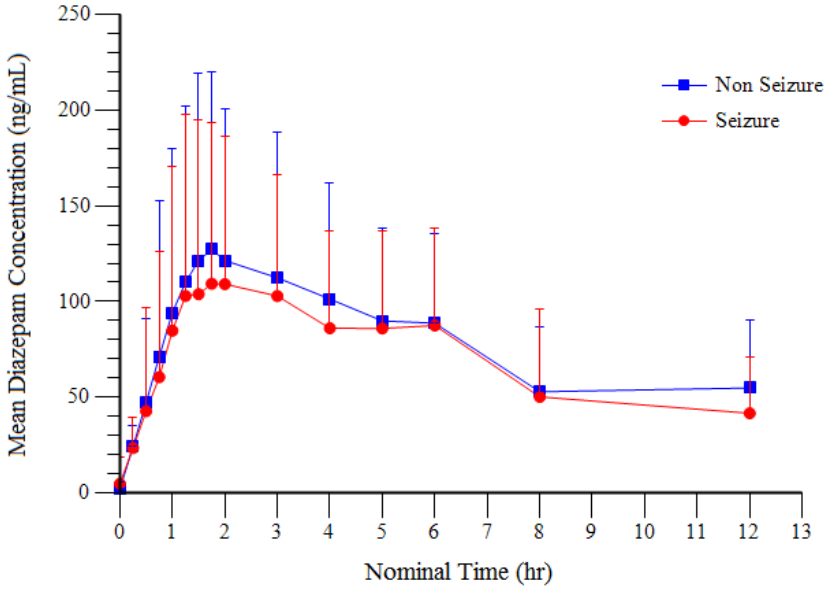
Forty-one (41) subjects had completed the study and 9 subjects were dosed ongoing as of the interim data analysis 1 cutoff date.

The PK analysis population included 34 subjects who completed the study through the 6-hour PK sampling periods on at least one of the dosing days and were included in the primary PK analysis and preliminary efficacy assessment. No subjects were excluded from PK analyses; the remaining 16 subjects were still on study as of this interim analysis. The PK Analysis Population

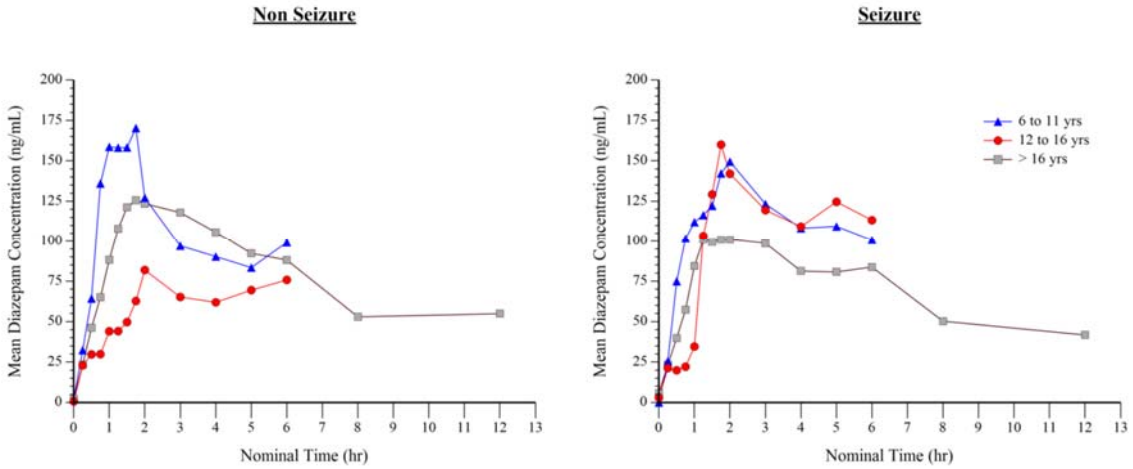
(N=34) was further analyzed by age groups: 6-11 years old (n=4), 12-16 years old (n=2) and >16 years old (n=28).

Following figure represents mean plasma concentration versus time profiles of diazepam, sorted by condition on linear scale.

Mean Plots of the VALTOCO Nasal Spray Plasma Concentration versus Time Curves: Separated by condition



Mean Plasma Concentration versus Time Profiles of Diazepam by Age Group, Sorted by Condition.



Note: There were only 2 subjects included in PK analysis population in 12 to 16 years age group. Whereas in 6 to 11 years and >16 years age groups there were 4 and 28 subjects, respectively. The individual AUCs in patients during seizure (ictal or periictal) or non-seizure (normal state) of 12 to 16 years age group were within the AUC range for >16 years age group.

Following tables represents diazepam pharmacokinetic parameters for 15 mg and 20 mg Diastat.

Summary Statistics of Diazepam Pharmacokinetic Parameters, Sorted by Condition (Non-seizure, seizure)

Status	Statistic	AUC_{0-6} (hr•ng/mL)	C_{max} (ng/mL)	t_{max} (hr)	t_{lag} (hr)	AUC_{0-t} (hr•ng/mL)
Non-seizure	N	34	34	34	34	34
	Mean	566	179	2.74	0.00	606
	SD	295	104	2.19	0.00	320
	Min	107	23.2	0.467	0.00	108
	Median	571	167	2.00	0.00	581
	Max	1140	386	12.0	0.00	1290
	CV%	52.2	57.8	80.1	–	52.8
	Geo Mean	474	145	2.18	–	512
	GCV%	73.9	84.8	75.4	–	70.1
Seizure	N	34	34	34	34	34
	Mean	518	156	3.31	0.00	571
	SD	300	86.2	2.48	0.00	307
	Min	18.7	4.20	1.00	0.00	39.8
	Median	438	136	2.21	0.00	442
	Max	1330	377	12.3	0.00	1330
	CV%	57.9	55.1	74.8	–	53.7
	Geo Mean	424	127	2.66	–	488
	GCV%	88.8	96.9	73.0	–	70.7

Abbreviations: CV = coefficient of variation, Geo = geometric, GCV = geometric coefficient of variation, Max = maximum, Min = minimum.

Statistical Comparison of Diazepam with Respect to Cmax and AUC0–6 under Seizure and Normal Conditions

Ln (PK Parameter)	Geometric Mean Ratio (%)	Lower 90% CI	Upper 90% CI
$Ln(AUC_{0-6})$	89.4	73.8	108.3
$Ln(C_{max})$	87.7	69.2	111.1

Abbreviations: CI = confidence interval.
Note: Non-seizure is the reference and seizure is the test.

To compare the results of this study conducted in epileptic patients to healthy subjects from previous studies (DAIZ.001.02 and DIAZ.001.03), the AUC0-6 and Cmax were dose normalized to a 10-mg dose/70 kg subject.

Comparison of Diazepam PK parameters (Cmax and AUC0–6), Healthy versus Non-seizure and Seizure Subjects

Reference	Test	Ln (Dose-normalized PK Parameter	Geometric Mean Ratio (%)	Lower 90% CI	Upper 90% CI
Healthy	Non-seizure	Ln(AUC_{0-6} Dose-normalized)	74.7	60.0	93.0
		Ln(C_{max} Dose-normalized)	65.6	51.8	83.1
Healthy	Seizure	Ln(AUC_{0-6} Dose-normalized)	66.8	53.1	84.2
		Ln(C_{max} Dose-normalized)	57.6	45.0	73.7

Abbreviations: CI = confidence interval.

Note: This is a cross-study comparison of data from Studies DIAZ001.02 and DIAZ001.03 with the current study.

CONCLUSIONS:

- The mean PK profiles appeared similar with a large overlap following IN administration of Valtoco in patients during seizure (ictal or periictal) or non-seizure (normal state).
- Comparison of epileptic patients to that of normal healthy subjects indicated that patients with epilepsy had lower levels of diazepam (AUC lower ~ 25% to 33% and Cmax ~34% to 42%) compared to healthy subjects. This reduction in patients AUC and Cmax may be due to concomitant inducers.

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/s/

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