# NEURELIS, INC.

# INVESTIGATIONAL NEW DRUG PROTOCOL

# NRL-1 (INTRANASAL DIAZEPAM)

**PROTOCOL NUMBER DIAZ.001.04**
**VERSION 5**
**02 MAY 2017**

**AN OPEN-LABEL, REPEAT-DOSE PHARMACOKINETIC STUDY OF NRL-1 IN EPILEPSY SUBJECTS UNDER SEIZURE AND NORMAL CONDITIONS**

**SPONSOR:**

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# CONFIDENTIAL

## KEY CONTACTS FOR THE STUDY

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# TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES



## LIST OF APPENDICES

# LIST OF ABBREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| AE | adverse event |
| AEDs | antiepileptic drugs |
| ARS | acute repetitive seizures |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| $AUC_{(0-6)}$ | area under the plasma concentration time-curve to 6 hours post dose |
| $AUD_{(0-\infty)}$ | area under the plasma concentration time-curve to infinity |
| ß-hCG | serum pregnancy test |
| BLQ | below the limit of quantitation |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| ºC | Degrees Celsius |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CBC | complete blood count |
| CFR | Code of Federal Regulations |
| CFSAN | Center for Food Safety and Nutrition |
| cGMP | current Good Manufacturing Practices |
| CI | Confidence interval |
| cm | Centimeter |
| $C_{max}$ | Maximum plasma concentration |

| ABBREVIATION | DEFINITION |
|---|---|
| CNS | central nervous system |
| $CO_2$ | bicarbonate/carbon dioxide |
| CRF | case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Cofficient of variation |
| ECG | Electrocardiogram |
| *E.coli* | *Escherichia coli* |
| EEG | Electroencephalogram |
| EDTA | ethylenediaminetetraacetic acid |
| EMU | Epilepsy Monitoring Unit |
| EPA | Environmental Protection Agency |
| ºF | Degrees Farenheit |
| FDA | US Food and Drug Administration |
| GABA | gamma-aminobutyric acid |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMR | Geometric mean ratio |
| GRAS | generally recognized as safe |
| H | Hour |
| HbSAg | Hepatitis B surface antigen |
| HED | human equivalent dose |
| HEENT | head, ears, eyes, nose, and throat |

| ABBREVIATION | DEFINITION |
|---|---|
| HIV | human immunodeficiency virus |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IM | intramuscular |
| IP | investigational product |
| IRB/EC | Institutional Review Board/Ethics Committee |
| IUD | intrauterine device |
| IV | intravenous |
| kg | kilogram(s) |
| L | Liter |
| LC/MS/MS | Liquid chromatography tandem mass spectrometry |
| $LD_{50}$ | lethal dose 50% or median lethal dose |
| LDH | lactate dehydrogenase |
| MRHD | maximum recommended human dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram(s) |
| min | Minute |
| mL | milliliter |
| mm | Millimeter |
| NIH | National Institutes of Health |
| NOEL | no observable effect level |
| NRL-1.A | 100 mg/mL diazepam nasal spray suspension manufactured for Neurelis, Inc. |

| ABBREVIATION | DEFINITION |
|---|---|
| NRL-1.B | 100 mg/mL diazepam nasal spray solution manufactured for Neurelis, Inc. |
| OTC | Over-the-counter |
| OECD | Organisation for Economic Co-operation and Development |
| PBMC | blood peripheral mononuclear cells |
| PI | principal investigator |
| PK | pharmacokinetics |
| QTcF | Corrected QT interval, Fridericia's formula |
| RBC | red blood cell |
| SAE | serious adverse event |
| SOP | standard operating procedure |
| SD | Standard deviation |
| TEAE | treatment-emergent adverse event |
| $t_{1/2}$ | Half-life |
| $t_{max}$ | time to maximum plasma concentration |
| UDS | Unit dose sprayer |
| µL | microliter |
| US/USA | United States of America |
| VAS | Visual Analog Scale |
| WBC | white blood cell |
| WHODD | World Health Organization Drug Dictionary |

## INVESTIGATOR STATEMENT

I have read and understand the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines, all applicable government regulations, and the International Conference on Harmonisation Good Clinical Practice Guidelines E6 (ICH-GCP).

I will maintain accurate source documents from which data are transcribed onto case report forms and accurate drug accountability records that show the receipt and disposition of all study drugs.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study.

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/EC prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB-approved Informed Consent Form is obtained from each subject prior to initiation of any study procedures.

I will report (within 24 hours) any serious adverse event, regardless of relationship to study drug, or pregnancy that occurs during the course of the study, in accordance with the procedures described in Section 11.0 of the protocol. I will notify the Sponsor if I become aware that a partner of a study subject becomes pregnant while the subject was receiving this study drug.

I will submit all protocol inclusion/exclusion violations to the Medical Monitor for approval prior to enrollment of the subject in the study.

I will allow the Sponsor, Neurelis, Inc. (Neurelis) and its agents, as well as the United States (U.S.) Food and Drug Administration (FDA) and other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the Sponsor as soon as possible thereafter (no later than one week).

This protocol contains information that is proprietary to Neurelis. The information contained herein is provided for the purpose of conducting a clinical trial for Neurelis.

The contents of this protocol may be disclosed to study personnel under your supervision and to your IRB/EC. The contents of this protocol may not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without the prior written approval of Neurelis.

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Investigator's Signature Date

## PROTOCOL SYNOPSIS

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| **Study Title** | An Open-Label, Repeat-Dose Pharmacokinetics Study of NRL-1 in Epilepsy Subjects Under Seizure and Normal Conditions (DIAZ.001.04) |
| **Phase** | Phase 1 (Pharmacokinetics in Epilepsy Subjects) |
| **Study Drug** | NRL-1 (Intranasal Diazepam) |
| **Objectives** | Primary objective:<br>• The primary objective of this study is to assess the pharmacokinetics (PK) of diazepam after single intranasal doses of NRL-1 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 will be the maximum plasma concentration ($C_{max}$) and the area under the curve through 6 hours ($AUC_{(0-6)}$).<br>Secondary objective:<br>• To compare the diazepam $C_{max}$, time to peak concentration ($t_{max}$) and $AUC_{(0-6)}$ after single administration of NRL-1 in Epilepsy subjects during the ictal or peri-ictal period to that after administration of NRL-1 to the same subjects under normal conditions;<br>• To compare the diazepam $C_{max}$, $t_{max}$, and $AUC_{(0-6)}$ after single administration of NRL-1 between Epilepsy subjects ages 6 to 11 and those greater than 12 years of age;<br>• To compare the diazepam $C_{max}$, $t_{max}$, and $AUC_{(0-6)}$ after single administration of NRL-1 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;<br>• To assess the safety and tolerability of diazepam after intranasal administration of NRL-1. |

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| **Study Design** | This is 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. Two doses of intranasal NRL-1 will be administered at either 5 mg, 10 mg, 15 mg, or 20 mg based on the subject's body weight. The study consists of a screening period, a baseline period, and a post-dose follow-up period. The NRL-1 dose will be administered during the ictal or peri-ictal period (Treatment 1), and again under normal non-seizing (intra-ictal) conditions (Treatment 2). The dosing may be done in either order (Treatment 1 or 2 first) with approximately 14-day wash-out between doses. Follow-up telephone contacts will be conducted 7-days and 14-days after the last dose of NRL-1. Between doses of NRL-1, subjects and caregivers should avoid the use of other diazepam containing products. For subjects who will roll over to the DIAZ.001.05 long term safety study, the Day 14 (second dosing day for NRL-1) assessments can be used as baseline assessments for DIAZ.001.05 to allow subjects to initiate long term treatment under that protocol.<br><br>Baseline in period 1 for this study is considered the period within 7 days of admission. The subject will be admitted and observed in the clinical site (i.e. Epilepsy Monitoring Unit [EMU] or Clinical Trial Research Center [CTRC]) and dosing will occur at the time of a seizure that is considered suitable for administration of NRL-1. All subjects will be monitored by EEG, which is considered standard of care in the EMU but part of the study procedure in the CTRC, with the start and stop time of the seizure being recorded based on the EEG. Time point 0 will be defined as the time of dosing of NRL-1 and initiation of PK blood sampling. Subjects with diazepam blood levels at baseline that are equal or greater than 10% of the $C_{max}$ will be excluded from the primary PK analysis set.<br><br>Treatment 1 with NRL-1 will be administered under ictal or peri-ictal conditions in a clinical setting to subjects having partial or generalized Epilepsy with motor seizures or seizures with clear alterations of awareness. Since the primary objective is to obtain diazepam plasma concentrations and PK information when the drug is given in the ictal or peri-ictal period, dosing of NRL-1 will ideally occur within 5 minutes after the onset of the seizure. The stop time of the seizure and any recurrence of seizure activity within the first 12 hours after dosing NRL-1 will also be recorded.<br><br>A 3 mL blood sample for PK will be collected at the baseline and at the post-dose period once admitted to the clinical site. During the post-dose period, 3 mL blood samples will be collected at predetermined times after NRL-1 dosing to determine the diazepam plasma concentration versus time profile. If the baseline pre-dose blood sample is unable to be collected, i.e., subject experiences a seizure prior to collection, then the pre-dose assessment closest to dosing will be included in the analysis.<br><br>If the subject experiences a seizure after NRL-1 dosing (during the blood sampling period), PK blood draws will be suspended as long as required for the subject's medical care and should resume when clinically feasible. Subjects may be treated with any other medication that does not contain diazepam that is standard of care. If the subject experiences a seizure after NRL-1 dosing and is administered an exclusionary medication (such as intravenous [IV], oral or rectal diazepam), PK blood draws will be stopped time of dosing diazepam recorded, and the Sponsor will be notified. All other safety procedures will be performed as per the protocol Schedule of Study Procedures (APPENDIX A). |

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| | The second treatment (Treatment 2) with NRL-1 will occur when the subject is in a normal state (intra-ictal period). Please note that it is not anticipated that subjects will be admitted to the clinical site for Treatment 2 and the site will select an appropriate clinical facility for this portion of the study. Subjects should be seizure free for at least 12 hours prior to dosing. A 3 mL blood sample for PK will be collected at the post-dose period in the clinic prior to administration of NRL-1. During the post-dose period, 3 mL blood samples will be collected at predetermined times after NRL-1 dosing to determine the diazepam plasma concentration versus time profile.<br>Treatment 1 and Treatment 2 may be given in either order, provided there is at least a 14-day wash out period between doses of NRL-1 and no other diazepam containing products are used between the two NRL-1 administrations.<br><br>Safety assessments include physical and neurological examination including head, ears, eyes, nose, and throat (HEENT), vital signs, laboratories (hematology, serum chemistry, and urinalysis), 12-lead electrocardiograms (ECGs), and adverse event (AE) assessment. Concomitant medications will be recorded. Columbia-Suicide Severity Rating Scale (C-SSRS for adults or children), nasal irritation assessment, assessment of mucosalerythema, mucosal edema, nasal discharge, mucosal crusting and mucosal epistaxis, sedation score assessment, and smell test (National Institutes of Health [NIH] Toolbox Odor Identification Test, (1, 2) will be conducted. |
| **Extension Study** | Subjects completing both periods of dosing and PK assessments as a participant in this protocol, are eligible for the long-term safety study (DIAZ.01.05) and may receive treatment with NRL-1 under that protocol. |
| **Sample Size** | Approximately 45 subjects, 15 subjects age 6 to 11 years, and 30 subjects over 12 years of age, are to be enrolled as part of this study with dosing during the ictal or peri-ictal period of a seizure. Of these, at least 10 adult subjects and 5 pediatric subjects will have PK assessments after dosing during the ictal period. |
| **Study Population** | Subjects with a clinical diagnosis of epilepsy who, in the opinion of the Investigator, may need a benzodiazepine for seizure control. |

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| **Main Inclusion Criteria** | Subjects must meet **All** of the following inclusion criteria to be enrolled in this study:<br>1. Male and female subjects between the ages of 6 and 65 years, inclusive.<br>2. Written informed consent to participate in the study.<br>3. Body mass index (BMI) not to exceed 35 kg/m², inclusive.<br>4. Subject has a clinical diagnosis of Epilepsy and, in the opinion of the Investigator, may need benzodiazepine intervention for seizure control.<br>5. Subjects having either partial or generalized Epilepsy with motor seizures or seizures with clear alteration of awareness are eligible for enrollment.<br>6. Female subjects of childbearing potential, defined as having a menstrual cycle and who are not surgically sterile or less than two (2) years postmenopausal, must complete a pregnancy screen and agree to utilize one of the following forms of contraception during the trial and for 21 days after the last dose of study drug: abstinence, hormonal (oral, transdermal, implant, or injection), barrier (condom, diaphragm with spermicide), intrauterine device (IUD), or vasectomized partner (six months minimum).<br>7. No clinically significant abnormal findings in the medical history, on the physical examination, ECG (corrected QT interval [QTcF] < 450 msec for males and QTcF < 470 msec for females), or clinical laboratory results during screening.<br>8. Subjects and caregivers must agree to return to the study site for all study visits and must be willing to comply with all required study procedures. |

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| **Main Exclusion Criteria** | Subjects must **NOT** meet any of the following Exclusion criteria to be eligible for enrollment:<br>1. Subject is undergoing intracranial EEG monitoring.<br>2. A history of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, severe seasonal or non-seasonal allergies, nasal polyps or any nasal passage abnormality that could interfere with nasal spray administration, or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results.<br>3. Subject has had significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening.<br>4. Subjects with active major depression or a past suicide attempt documented on the Baseline/Screening C-SSRS. The children C-SSRS should be used for subjects age 6 to 11. The adult C-SSRS should be used for subjects 12 and greater years of age.<br>5. Any Suicidal Ideation of 3, 4, or 5 or any Suicidal Behavior in Lifetime using C-SSRS.<br>6. A history of allergic or adverse responses to diazepam or any comparable or similar product.<br>7. Subjects who (for whatever reason) have been on an abnormal diet (such as one that severely restricts specific basic food groups [e.g., ketogenic diet], limits calories [e.g., fast], and/or requires the use of daily supplements as a substitute for the foods typically eaten at mealtimes), during the four (4) weeks preceding the study.<br>8. Subjects who donated blood or plasma within 30 days of the first dose of study drug.<br>9. Participation in a clinical trial within 30 days prior to the first dose of study drug. Participation in an observational (non-interventional) study is not excluded as long as there are no scheduling conflicts with this study.<br>10. Inadequate or difficult venous access that may jeopardize the quality or timing of the PK samples.<br>11. Female subjects who are trying to conceive, are pregnant, or are lactating.<br>12. Positive serum pregnancy test (ß-hCG) at screening or urine pregnancy test prior to each administration of study drug for all women of childbearing potential.<br>13. Positive blood screen on subjects age 12 or greater for human immunodeficiency virus (HIV), Hepatitis B surface antigen (HbSAg), or Hepatitis C, or a positive urine screen for alcohol, drugs of abuse, or cotinine. When marijuana was used for medical reasons in the opinion of the investigator, it is not considered as drug abuse and the patient can be enrolled even if the marijuana metabolites in the urine revealed as positive.<br>14. Treatment with phenobarbital or primidone within 30 days of the anticipated dosing visit (i.e., baseline).<br>15. Treatment with warfarin or dabigatran or other blood thinners within 30 days of the anticipated dosing visit (i.e., baseline).<br>16. Treatment with any diazepam containing products within 14 days of the anticipated dosing visit (i.e., baseline). |

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| | 17. Use of nasal decongestants or nasal steroids within 7 days prior to the screening visit or during the study.<br>18. Subject does not have the flu, rhinitis or any other nasal condition that would impact absorption of intranasal diazepam. |
| **Other Restrictions** | 1. Treatment with any known strong or moderate inhibitors or inducers of metabolizing enzymes (e.g., CYP-P450 enzymes or MAO) within fourteen (14) days prior to the first dose of NRL-1, or during the study, is prohibited without approval from the Medical Monitor (See APPENDIX E for list of prohibited medications).<br>2. Use of OTC oral and/or nasal decongestants within 7 days prior to the first dose of study drug or during the study.<br>3. Smoking and the use of tobacco products in excess of 10 cigarettes or 1 cigar per day is not permitted for one (1) month prior to the first dose of Study Drug and for the duration of the study. When marijuana was used for medical reasons in the opinion of the investigator, it is not considered as drug abuse and the patient can be enrolled even if the marijuana metabolites in the urine revealed as positive.<br>4. Subjects should not engage in strenuous exercise during the confinement period of the study. |

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| **Dosage and Administration of Study Drug** | The dose of 5 mg, 10 mg, 15 mg, or 20 mg of NRL-1 will be selected according to the subject's weight (rounded to the nearest kg) based on the following:<br>For Children Age 6-11 Years:<br>• 10 kg to 18 kg body weight will receive a 5 mg dose (50 mg/mL, 100 µL) administered as one spray in the left nostril.<br>• 19 kg to 37 kg will receive a 10 mg dose (100 mg/mL, 100 µL) administered as one spray in the left nostril.<br>• 38 kg to 55 kg will receive a 15 mg dose (75 mg/mL, 100 µL) administered as two 7.5 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).<br>• 56 kg to 74 kg will receive a 20 mg dose (100 mg/mL, 100 µL) of NRL-1 administered as two 10 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).<br>For Age 12 Years or greater:<br>• 14 kg to 27 kg body weight will receive a 5 mg dose (50 mg/mL, 100 µL) administered as one spray in the left nostril.<br>• 28 kg to 50 kg will receive a 10 mg dose (100 mg/mL, 100 µL) administered as one spray in the left nostril.<br>• 51 kg to 75 kg will receive a 15 mg dose (75 mg/mL, 100 µL) administered as two 7.5 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).<br>• Greater than 76 kg will receive a 20 mg dose (100 mg/mL, 100 µL) of NRL-1 administered as two 10 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril). |

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| **Safety Analysis** | AEs will be collected and reviewed to evaluate the safety and tolerability of diazepam nasal solution. Other safety measures will include physical examination, neurological examination, vital sign measurement, and clinical laboratory tests. AE collection will begin after baseline assessments are complete prior to the initial treatment with NRL-1 and continue for 14-days after the final dose. AE may be either spontaneously reported or elicited during questioning and examination of a subject. AE information will be elicited at appropriate intervals by indirect questioning using a non-leading question. Subjects will receive follow-up phone calls approximately 7 days (± 2 days) and 14 days (± 3 days) after the second dose of NRL-1 dosing to determine if any AE has occurred and to follow-up on any treatment-emergent AEs (TEAE[s]) ongoing since last communication with the subject.<br><br>Objective evaluations of nasal irritation will be assessed by a trained observer after administration of the intranasal formulation. Nasal irritation will also be evaluated prior to each administration of NRL-1 (baseline) and at 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge. Mucosal erythema, mucosal edema, nasal discharge, mucosal crusting and mucosal epistaxis will be evaluated on separate scales prior to each dose of NRL-1 (baseline), and at 30 (± 10 min) minutes, and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge. The subjects will also be required to report any incident of nasal irritation or mucosal epistaxis in-between evaluation time points and during follow up contacts.<br><br>Objective evaluations of sedation will be made using a 6-point ($0 \rightarrow 5$) sedation scoring system that will be used to assess the degree of drowsiness of the subjects after administration of the intranasal formulation. Sedation scores will be reported by the subject (if awake) as well as by a trained observer, using the same rating scale, prior to (baseline) and at 15 (± 5 min) and 30 (± 10 min) minutes, and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose after each administration, and at discharge. Subjects will be also be questioned by the trained observer regarding their degree of drowsiness.<br><br>An unconstrained visual analog scale (VAS) that consists of a 10 cm (100 mm) horizontal straight line will be used to assess acute pain following administration of study drug. The ends of the scale are defined as extremes limits of pain sensation: 0 = no pain, 10 = extreme pain. The subjects will be asked to mark a point on the scale which best describes their intensity of pain and discomfort prior to (baseline) and at 15 (± 5 min) and 30 (± 10 min) minutes, 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post-dose, and at discharge. The location of the marking at each time point will be measured and noted as the reported score.<br><br>The C-SSRS, a measure of suicidal ideation and behavior, will be used to document suicidality in order to classify suicidal events. The children C-SSRS should be used for subjects age 6 to 11. The adult C-SSRS should be used for subjects 12 and greater years of age. Suicidality will be assessed at screening and baseline (pre-dose) and post-dosing at 6 hours. The screening and baseline assessments will use the **Baseline/Screening Phase 1** version of the C-SSRS. The **Since Last Visit** version of the C-SSRS will be used for post-dosing assessments.<br><br>Smell tests will be conducted at baseline, at 1 (± 15 min) hour, 4 (± 30 min) hours, and 24 (± 30 min) hours (before discharge) following NRL-1 administration. The NIH Toolbox Odor Identification Test will be used as smell tests. |

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| | Safety data will be summarized and descriptive statistics will be provided for actual values and change from baseline values for physical and neurological examination including HEENT, vital signs, clinical laboratory tests (serum chemistry, hematology, and urinalysis), and C-SSRS assessments.<br>The incidence and severity of TEAEs reported during the study and their relationship to study drug will be tabulated. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by body system.<br>The World Health Organization Drug Dictionary (WHODD) will be used to classify prior and concomitant medications by therapeutic class and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class by dose cohort. |
| **Pharmaco-kinetic Analysis** | Blood samples (3 mL) will be collected in this study to measure diazepam plasma concentrations following the intranasal administration of NRL-1. All subjects will have samples collected through at least 6 hours after each of the two doses of NRL-1. Blood samples for PK will be 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 should also be obtained if feasible at 8 and 12 hours after dosing. If a blood sample collection is delayed, then the collection will occur as soon as feasible and should not be 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.<br>The following PK parameters for diazepam will be calculated using non-compartmental analysis: $C_{max}$, $t_{max}$, $AUC_{(0-6)}$ with a concentration equal to or greater than the lower limit of quantitation.<br>If a second dose of NRL-1 is administered due to a subsequent seizure between 4 and 12 hours after the initial dose, when clinically feasible, PK samples should be collected based on the time of the second dose at 0 (immediately after the $2^{nd}$ dose), 30 minutes, and 1, 2, and 4 hours after dosing.<br>For Treatment 1, the actual time of seizure onset, dose of NRL-1, time of seizure stop, and time of each blood sample will be recorded. PK parameters will be determined using actual times of sample collection relative to the administration of NRL-1. |

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| **Statistical Analysis** | Individual subject plasma concentrations, actual sampling times, and PK parameters will be listed by analyte and treatment. Descriptive statistics will be 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 will be 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 will be displayed on linear and semi-logarithmic axes.<br>A separate but identical analysis will be performed on the observed PK parameters depending on which age group the subject belongs. The PK parameters $C_{max}$ and $AUC_{(0-6)}$ for diazepam will be compared for the first dose of NRL-1 under seizing conditions to the second dose of NRL-1 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. $C_{max}$ and $AUC_{(0-6)}$ will be normalized to the 10 mg dose prior to analysis. Confidence intervals (CI) (90%) will be 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 will be exponentiated back to the original scale. Dose equivalence will be concluded if the 90% CI for the GMRs among the two comparisons of the two parameters fall within 80% to 125%.<br>For $AUC_{(0-6)}$ and $C_{max}$, the geometric mean (inverse log-transformed) and the 90% CI for geometric means will be compared to those observed in DIAZ.001.02 and DIAZ.001.03 studies.<br>The $C_{max}$ and $AUC_{(0-6)}$ determined in epilepsy subjects in the ictal and peri-ictal period will be compared between the same subject in a normative state. The $C_{max}$, $t_{max}$, and $AUC_{(0-6)}$ determined in epilepsy subjects will also be compared to those results in healthy, non-seizing, volunteers.<br>The $C_{max}$ and $AUC_{(0-6)}$ will be visually compared between the two age groups in both seizure/non-seizure conditions. |
| **Study Duration** | It is planned that each subject will participate in the study for approximately 49 to 65 days, which comprises a 21 day screening period, first treatment period and wash out of 14 days (28 days if on oral contraceptives), second treatment period and follow up period of 14-days. The actual treatment periods will be approximately 28 to 42 days. |
| **Study Centers** | Up to sixteen (16) experienced centers will enroll patients. |

## 1.0 INTRODUCTION

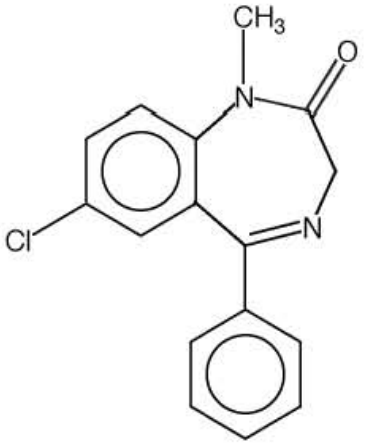
Epilepsy is a significant health problem affecting 50 million people worldwide, including 2.7 million Americans. Epilepsy negatively impacts quality of life and increases morbidity and mortality. In the US, 25-50,000 deaths each year are attributed to seizures and related causes.

Seizure emergencies include acute repetitive seizures (ARS), which are defined as intermittent increases of seizure activity while on stable regimens of antiepileptic drugs (AEDs). The intravenous (IV) formulation of diazepam has been used for over 30 years in the treatment of seizure emergencies, including status epilepticus, but the current standard of care for ARS is a rectal gel formulation of diazepam, Diastat® (3).

Diastat rectal gel was approved for marketing by the United States (US) Food and Drug Administration (FDA) in 1997 and is the only diazepam formulation in the US that is approved for ARS. Although Diastat has an excellent post-approval safety profile and is highly effective in the management of ARS, the product is considered inconvenient and cumbersome, particularly for adult patients, because use of the product requires rectal administration by the caregiver. Due to this route of administration, the use of Diastat has been limited primarily to the pediatric population, ages 2-12 years.

Diazepam, illustrated in Figure 1 below, is a benzodiazepine anticonvulsant with the chemical name; 7-chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one. It is a colorless to light yellow crystalline compound, insoluble in water. The empirical formula is $C_{16}H_{13}ClN_2O$ and the molecular weight is 284.75.

**Figure 1: Diazepam**




Neurelis is investigating NRL-1 for the treatment of ARS as an alternative, more convenient to use product than the current standard of care, Diastat rectal gel, which is administered rectally at

the time of occurrence of an acute seizure. Two different formulations of NRL-1 were evaluated in an absolute bioavailability study to assess the best absorption profile between a suspension formulation (NRL-1.A) and a solution formulation (NRL-1.B). This initial pharmacokinetics (PK) study demonstrated that the solution formulation of NRL-1 gave the best PK characteristics with over 97% absolute bioavailability versus the IV diazepam, and was most comparable to the Diastat rectal gel PK profile reported in the label. As a result of this PK study, Neurelis will pursue additional studies with NRL-1 to evaluate the safety and PK characteristics of a final commercial product.

NRL-1 is a novel formulation that includes a proprietary functional excipient called Intravail® A3, supplied by Aegis Therapeutics. Intravail A3 is a GRAS (Generally Recognized as Safe) excipient that is being evaluated in low concentrations (less than 1%) to improve the bioavailability of drugs administered by the intranasal route. The absorption enhancing properties of alkylglycoside surfactants, such as Intravail A3, are believed to occur via loosening of the tight junctions (paracellular) coupled with the fluidization and penetration of cell membranes (transcellular) causing increased drug movement into the cell (4). The NRL-1 formulation was found to have an optimal bioavailability with the addition of 0.25% Intravail A3.

A Phase 1 study with NRL-1 was completed in healthy volunteers to evaluate the absorption and PK of two different formulations. The primary objective of this study was to assess the bioavailability and PK of diazepam after intranasal administration of suspension and solution formulations compared to IV administration to healthy volunteers under fasted conditions. The secondary objective of this study was to assess the safety and tolerability of two formulations of diazepam nasal spray after a single intranasal administration of each formulation.

Based on the pilot PK work completed, it is anticipated that NRL-1 will provide comparable exposures of diazepam by the intranasal route of administration to that observed with Diastat rectal gel. Intranasal delivery is anticipated to be a more convenient and more acceptable route of administration for patients and their caregivers.

### 1.1 Nonclinical Assessments

Given the clinical history of diazepam, the pharmacology, toxicology, and general safety are well understood. Since it was first approved for marketing more than 40 years ago, a large amount of the relevant data on the safety and efficacy of diazepam is derived from clinical use. The following section provides a brief overview of the literature and public information on the nonclinical safety of diazepam for the benefit of the investigator.

Neurelis has conducted animal PK studies to assess the bioavailability and tolerability of the NRL-1 formulations intended for use in clinical studies. These studies were conducted in rats, rabbits, and dogs. No unexpected or adverse clinical observations were noted in this study.

### 1.1.1 Pharmacology

Diazepam has anticonvulsant properties unique to some benzodiazepines and is the only product that is specifically approved for the treatment of ARS. Benzodiazepines act via micromolar benzodiazepine binding sites and significantly inhibit depolarization-sensitive calcium uptake in rat nerve cell preparations (5). Diazepam inhibits acetylcholine release in mouse hippocampal synaptosomes. This has been found by measuring sodium-dependent high affinity choline uptake in mouse brain cells *in vitro*, after pretreatment of the mice with diazepam *in vivo*. This may play a role in explaining diazepam's anticonvulsant properties (6). Diazepam binds with high affinity to glial cells in animal cell cultures (7). Diazepam at high doses has been found to decrease histamine turnover in mouse brain via direct action at the benzodiazepine-gamma-aminobuytric (GABA) receptor complex (8). Diazepam also decreases prolactin release in rats (9). Diazepam has no effect on GABA levels and no effect on glutamate decarboxylase activity, but has a slight effect on GABA transaminase activity (10).

Metabolism studies in animals and man have indicated that oral diazepam is rapidly absorbed from the gastrointestinal tract. Peak blood levels are reached within 1-2 hours after administration. The acute half-life is 6-8 hours with a slower decline thereafter, possibly due to tissue storage.

Limited data are available on nonclinical evaluations of diazepam in safety pharmacology studies for central nervous system (CNS) effects. However, diazepam has been extensively studied in humans and its effects on the CNS are well established clinically. Diazepam is a benzodiazepine with CNS depressant properties and a somewhat flatter dose-response slope than other sedative-hypnotic drugs. In laboratory animals, diazepam produces, in varying doses, taming, disinhibitory, sedative, anticonvulsant, muscle relaxant, ataxic, and hypnotic effects.

Diazepam is relatively devoid of autonomic effects and does not significantly reduce locomotor activity at low doses, nor depress amphetamine-induced excitation. In high doses, it activates the drug metabolizing enzymes in the liver. Diazepam also possesses dependence liability and may produce withdrawal symptoms, but has a wide margin of safety against poisoning.

Diazepam has a slight depressive effect on cardiovascular function, but is widely considered to have less cardiovascular liability than any other benzodiazepines.

### 1.1.2 Toxicology of NRL-1 and Diazepam

#### 1.1.2.1 Single Dose Toxicity Studies

The acute toxicity of diazepam is considered to be very low relative to other benzodiazepine compounds or other psychotropic drugs. Generally, after very large acute doses (more than 450 times the typical human dose), respiratory depression and failure are the primary causes of death in animals. Acute toxicology studies have been reported in the rat, dog, and mouse (11).

Based on these studies a median lethal dose ($LD_{50}$) for diazepam has been established or each species.

| | |
|---|---|
| $LD_{50}$ (oral) rat: | 1200 mg/kg |
| $LD_{50}$ (oral) dog: | 1000 mg/kg |
| $LD_{50}$ (oral) mouse: | 700 mg/kg |

#### 1.1.2.2 Repeated-Dose Toxicology Studies

The toxicology of diazepam is well understood in the literature and based on literature for approved marketed products.

During animal PK studies, a total of 12 formulations of diazepam with Intravail A3 concentrations up to 0.50% were evaluated in rabbits. These studies also included evaluation of clinical signs and symptoms of toxicology, as well as nasal irritation. During these studies with intranasal doses up to 10 mg/animal, no unexpected clinical signs of toxicity were observed, with the only notable effect of sedation being the expected pharmacological effect of diazepam. Gross pathology and histopathology evaluations of nasal mucosa from animals after sacrifice did not reveal signs of nasal irritation or other findings that were abnormal as compared to controls. Thus no significant toxicity or nasal irritation (of selected formulations within the two studies) was observed with any of the NRL-1 formulations tested in the rabbit.

Intranasal doses of NRL-1 non-aqueous solution were well tolerated in rats up to 1 mg/day (a 10 µL dose volume of 100 mg diazepam per mL) and dogs dosed with 20 mg/day (a 200 µL dose volume of 100 mg diazepam per mL). After intranasal administration of NRL-1 formulations to rabbits in single dose PK and tolerability studies, and to rats and dogs in non-Good Laboratory Practices (GLP) intranasal toxicity studies for 28 days, there were no significant signs of clinical effects to indicate acute irritation and after sacrifice there were no dose-limiting clinical observations or toxicologically important events. All dose levels were well tolerated with only minimal histopathological changes. A full summary of the repeat-dose toxicology studies is provided in the NRL-1 Investigator's Brochure.

The anticipated safety of the NRL-1 formulations is expected to be similar to diazepam dosed by rectal gel administration. Based on animal studies there does not appear to be any significant acute or chronic irritation of the nasal mucosa.

#### 1.1.2.3 Genotoxicity and Carcinogenicity Studies

Diazepam has been reported to have mutagenic activity in the Salmonella typhimurium tester strain TA100 in the Ames test (12). Little or no effect was seen in an assay for chromosomal aberrations, performed in Chinese hamster cells *in vitro* (13).

Studies by De la Iglesia *et al.* (14) have demonstrated no increase in tumors frequency after feeding diazepam, 75 mg/kg/day, to rats and mice for 104 and 80 weeks, respectively.

#### 1.1.2.4 Reproductive and Developmental Studies

Diazepam has been shown to be teratogenic in mice and hamsters when given orally at single doses of 100 mg/kg or greater (approximately eight times the maximum recommended human dose [MRHD = 1 mg/kg/day] or greater on a mg/kg basis). Cleft palate and exencephaly are the most common and consistently reported malformations produced in these species by administration of high, maternally-toxic doses of diazepam during organogenesis. Rodent studies have indicated that prenatal exposure to diazepam doses similar to those used clinically can produce long term changes in cellular immune responses, brain neurochemistry, and behavior (15).

### 1.1.3 Pharmacology and Toxicology of Intravail A3

The toxicokinetics and metabolism of alkylglycosides, such as Intravail A3 (dodecylmaltoside), have been studied in detail under Organisation for Economic Co-operation and Development (OECD) Guidelines for Testing of Chemicals. Orally and nasally administered alkylglycosides are hydrolyzed to glucose and the corresponding long chain alcohol. No toxic metabolites are formed at any stage in the metabolic process. Dodecyl maltoside is a component (up to approximately 25%) of a mixture of alkylglycosides that are the subject of an application for GRAS status designation by the US FDA Center for Food Safety and Nutrition (CFSAN) and the US Environmental Protection Agency (EPA) based on their use as detergents or surfactants as a component of compounds in food industry and agricultural usages. With their use in these contexts, there is no established limitation on the oral or topical exposure allowed for humans.

Twenty (20) GLP nonclinical studies of the pharmacology and toxicology of Intravail A3 have been conducted by a number of investigators, as a single agent and in combination with pharmacologically active ingredients in *in vitro* studies and in rats, Guinea pigs, rabbits, dogs, and monkeys. Conclusions from the rat and rabbit studies include findings of a regenerative response typically seen following local irritation of nasal mucosa which may be attributed to the use of pipettes for dosing (most likely the result of whole droplet instillation), according to Charles Rivers pathologists. In contrast, nasal spray actuators were used for dosing in the dog and monkey toxicology studies (for delivery as a mist or fine plume representative of human administration), and these same findings were not observed. The pathologist concludes the effects were mild and reversible, and should be considered of minimal risk for clinical trial.

Spack *et al.* (16) evaluated Intravail A3 for its potential to cause genotoxicity in preclinical studies for use as a mucosal surface permeation enhancer of AG284, a protein peptide complex for the treatment of multiple sclerosis. Intravail A3 was tested in the bacterial reverse mutation assay using *S.typhimurium* and *Escherichia coli* (*E.coli)* tester strains. The maximum dose tested was 25 mg/plate. No positive response was observed and hence deemed not mutagenic at 0.5 mg/mL Intravail A3 was also tested in the chromosomal aberration assay using *in vitro* mammalian cytogenetic tests with human blood peripheral mononuclear cells (PBMCs). A dose range was established first and then its clastogenic potential was tested. The maximum

concentration tested was 50 mg/mL. No statistically significant increases were observed in either the non-activated or S9 activated test systems relative to the control group. Therefore, based on these findings, Intravail A3 was not considered a mutagen or genotoxic agent.

The dosage of NRL-1 that will be used in the current studies is based on patient weight ranges from the Diastat label. The NRL-1 doses administered in these clinical studies will be 5 mg dose for patients with a body weight < 20 kg, 10 mg dose for patients with a weight of 20 kg to ≤ 50 kg, a 15 mg dose for patients with a weight of > 50 to < 75 kg, and a 20 mg dose for patients with a weight ≥ 75 kg. The doses used in the clinical studies are supported by clinical experience and approved dosing given that the bioavailability of NRL-1 is 97%.

The NRL-1 formulation contains 0.25% Intravail A3 (0.025 mg/100 µL). Table 1 provides the calculated safety margins based on a rat no observable effect level (NOEL) of 80 µg/day and a dog NOEL of 330 µg/day for Intravail A3.

**Table 1: Intravail A3 Safety Margins Based on Current NRL-1 Formulation**

| Species | NOEL | Human Equivalent Dose (HED) | Intravail A3 Safety Margins |
|---|---|---|---|
| Rat | 0.32 mg/kg (80 µg/day) | 0.05 mg/kg | 74 - 144 fold |
| Dog | 0.036 mg/kg (330 µg/day) | 0.02 mg/kg | 55 - 28 fold |
| Human | | 0.00036 - 0.0007 mg/kg (0.025 mg/spray) | |

*based on weights for rat, dog, and humans as 0.25 kg, 9.1 kg, and 60 kg, respectively.

## 1.2 Clinical Experience (Diazepam and NRL-1)

Diazepam has been in clinical trials and human use for over 40 years by multiple routes of administration including intranasal and intravenous dosage forms. In general, the product has a good safety profile and has not been associated with any chronic or serious side effects in humans. Diazepam has been extensively studied and its PK and metabolism in humans is well understood. When administered orally, intravenously, or rectally, most of diazepam is extensively and rapidly absorbed, with bioavailability varying from 80 to 100 % and time to maximum plasma ($t_{max}$) concentration ranging from minutes (IV) to several hours (oral).

The safety of diazepam by the intranasal route of administration is also supported by the IV formulation as the IV route of administration gave the most rapid $t_{max}$ and highest maximum plasma concentration ($C_{max}$) of any other route of administration. Doses of diazepam by IV administration are safe up to 30 mg administered as a 20 to 30 minute infusion time in adults, according to the FDA product labeling. Given the bioavailability demonstrated for NRL-1 (97%) in the absolute bioavailability study in comparison to intravenous diazepam, it is considered that a dose of up to 20 mg of diazepam given by intranasal administration would not cause a safety concern even if completely and rapidly absorbed.

For IV diazepam, the US product labeling states that the usual recommended dose in older children and adults ranges from 2 to 20 mg by intramuscular (IM) or IV administration, depending on the indication and its severity. In some conditions, e.g., tetanus, larger doses may be required. For seizure emergencies, such as status epilepticus and severe recurrent convulsive seizures, IV doses of up to 30 mg diazepam administered over a 20 to 30 minute time period is approved for adults according to US FDA labeling. Thus, an intranasal dose of 20 mg of diazepam as NRL-1 should not present a significant safety risk to subjects.

### 1.2.1 Clinical Trials with NRL-1

An absolute bioavailability study of two formulations of NRL-1 has been completed. Study DIAZ.001.01 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 (if subjects are on oral contraceptives (OC) the period between dosing should be extended to approximately 28-days to ensure that the subject is dosed at the same approximate time of the OC cycle).

Subjects were randomized into 6 sequence groups with 4 subjects per sequence group. The sequence of the treatments was randomly assigned, and all subjects received each of the following diazepam 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

Diazepam was absorbed after intranasal administration of both proprietary formulations to humans, with higher exposure after administration as a solution (NRL-1.B) (absolute bioavailability 97%) than as a suspension (NRL-1.A) (absolute bioavailability 67%). With the exception of two subjects who had longer $t_{max}$ for the intranasal solution, $t_{max}$ was randomly distributed between the two intranasal treatments with comparable medians and ranges. The difference in exposure between the intranasal solution and intranasal suspension is therefore due to the extent rather than to the rate of absorption.

The mean elimination half-life ($t_{1/2}$) of diazepam was comparable for the two intranasal formulations of diazepam and the IV treatment indicating that there does not appear to be a prolonged absorption of diazepam after intranasal administration.

Differences between the solution and suspension with respect to the metabolite, desmethyldiazepam, were consistent with those for the parent compound. The mean (SD) metabolite-to-parent ratios of area under the plasma concentration-time curve to infinity ($AUC_\infty$), uncorrected for molecular weight, were 1.47 (0.28) for the intranasal solution and 1.49 (0.38) for the intranasal suspension, consistent with the ratio of 1.54 (0.43) for the IV. This suggests little

or no contribution to the extent of formation of desmethyldiazepam by first-pass metabolism and thus a low likelihood that any of the intranasal-administered diazepam was absorbed from the gastrointestinal tract after swallowing any "run off" from the back of the nose.

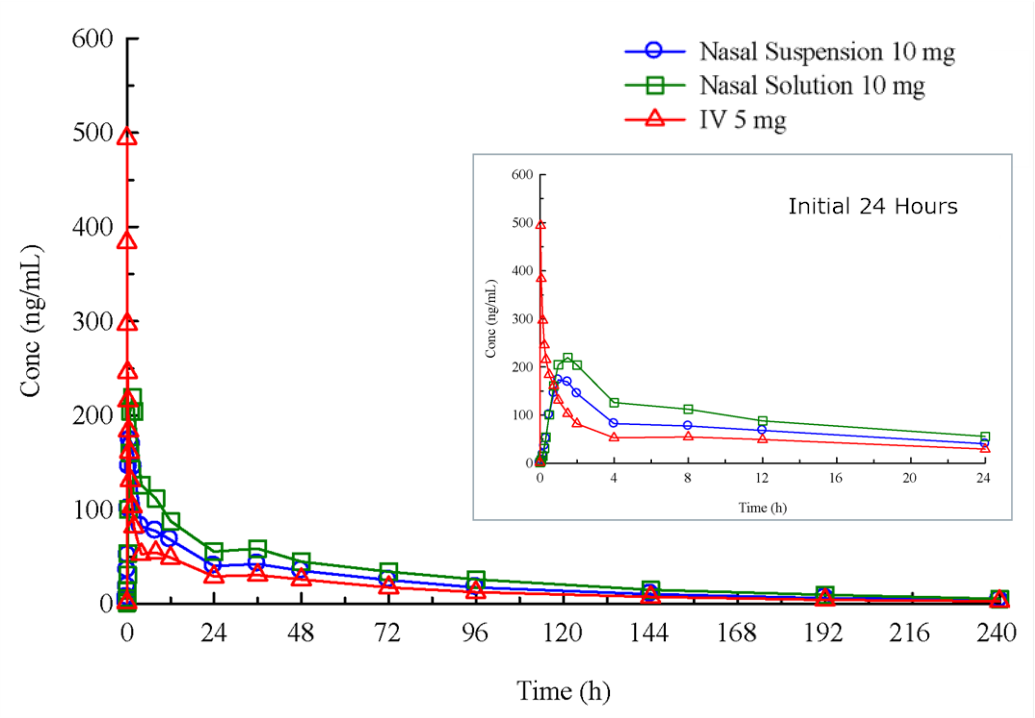
A summary of the PK data from the DIAZ.001.01 study is provided in Table 2 and Figure 2.

**Table 2: Summary of Pharmacokinetic Data from the DIAZ.001.01 Study**

| | 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) |
| t½ (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 $t_{max}$

**Figure 2: Arithmetic Mean Plasma Diazepam Concentrations (Inset Illustrates the Initial 24 Hours)**



The safety results show that administration of intranasal diazepam suspension (NRL-1.A), solution (NRL-1.B), and IV diazepam were well-tolerated. While most (71%) subjects experienced at least one treatment-emergent adverse event (TEAE) during the study, the frequency of adverse event (AE) occurrence did not appear to be dependent on diazepam formulation, and the AE profile provided no clear evidence of treatment differences. All TEAEs were considered by the Investigator to be of mild or moderate intensity.

Overall, the most frequently reported TEAEs were epistaxis (7 subjects) and somnolence (6 subjects). While AEs of somnolence were more commonly associated with IV diazepam (4 subjects) than with either of the intranasal diazepam formulations (1 subject each), sedation scores were similar across treatment groups at most post-dose time points.

For epistaxis, it is noteworthy that intranasal delivery of diazepam did not appear to be a predictor of epistaxis (or nasal irritation). The number of AEs of epistaxis was greater following IV diazepam (5 events) than after administration of NRL-1.A (1 event) or NRL-1.B (3 events). In addition, previous exposure to intranasal diazepam did not appear to influence the onset of nasal bleeding/irritation in the presence of IV diazepam exposure. In this study, nasal bleeding was identified after IV diazepam administration when subjects had no prior exposure to intranasal diazepam and when subjects' prior exposure to intranasal diazepam did not produce bleeding/irritation.

In addition to events of epistaxis and somnolence, other AEs reported for more than one subject overall included: headache (5 subjects), nasal discomfort (4 subjects) and nasal inflammation (3 subjects). No other AE was reported for more than one subject, either within a treatment group or overall.

There were no AE reports of nasal pain by any subject in any treatment period.

Of the 24 subjects who received study drug, 13 experienced at least one AE considered by the Investigator to be related to treatment. The most commonly experienced TEAEs were somnolence (6 events total), nasal discomfort (4 events total), headache (4 events total), and epistaxis (3 events total).

No subject was withdrawn from the study in response to an AE. No serious adverse events (SAEs) were reported, and no deaths occurred during the study. There were no clinically important findings noted in the vital sign data, electrocardiogram (ECG) findings, or in the individual clinical laboratory data. One subject had a clinically significant finding in the physical examination at the end of study assessment; this event, mouth ulceration (an AE), was considered by the Investigator to be both mild in severity and unrelated to study drug.

**Conclusion**

Overall, the results of past clinical studies and the long history of diazepam use in patients, support the proposed Phase 1 clinical trial for NRL-1 and the safety of the proposed intranasal doses of diazepam intended for this trial.

### 1.2.2 Pharmacokinetics and Product Metabolism in Humans

Oral Administration:

After oral administration, greater than 90% of diazepam is absorbed and the average time to achieve peak plasma concentrations is 1–1.5 hours with a range of 0.25 to 2.5 hours. Absorption is delayed and decreased when administered with a moderate fat meal. In the presence of food mean lag times are approximately 45 minutes as compared with 15 minutes when fasting. There is also an increase in the average time to achieve peak concentrations to about 2.5 hours in the presence of food as compared with 1.25 hours when fasting. This results in an average decrease in $C_{max}$ of 20% in addition to a 27% decrease in area under the curve (AUC) (range 15% to 50%) when administered with food.

In young healthy males, the volume of distribution at steady-state is 0.8 to 1.0 L/kg. The decline in the plasma concentration-time profile after oral administration is biphasic. The initial distribution phase has a half-life of approximately one hour, although it may range up to 3-hours (3).

Intravenous Administration:

IV administration of diazepam results in a $t_{max}$ at the end of the infusion time and $C_{max}$ dependent on the rate of infusion. Doses of 10 mg given over a 20 to 30 minute infusion time are common in clinical trials and practice. Doses of up to 30 mg in a 30 minute infusion time are allowed in the product labeling for IV diazepam.

Rectal Administration:

Diazepam rectal gel is well absorbed following rectal administration, reaching peak plasma concentrations in 1.5 hours. The absolute bioavailability of diazepam rectal gel relative to diazepam injectable according to the product labeling of Diastat is 90%. The volume of distribution of diazepam rectal gel is calculated to be approximately 1 L/kg. The mean $t_{1/2}$ of diazepam and desmethyldiazepam following administration of a 15 mg dose of diazepam rectal gel was found to be about 46 hours (Coefficient of variation [CV]= 43%) and 71 hours (CV = 37%), respectively (17).

Intranasal Administration:

Several clinical studies with intranasal formulations of diazepam have been reported in the literature. Generally, absolute bioavailability of these formulations was low (approximately 50%) and have been conducted in both healthy volunteers and patients with similar outcomes.

Gizurarson *et al.* administered a 2 mg dose of a 20 mg⁄mL diazepam solution dissolved in 5% glycofurol in polyethylene glycol 200. The mean bioavailability was 50.4 ± 23.3% with a time to peak concentration of 18 ± 11 minutes (18).

Lindhardt *et al.* evaluated an intranasal formulation of diazepam with doses of 4 mg and 7 mg in polyethylene glycol 300 in seven healthy volunteers as compared to a 5 mg intravenous dose. The intranasal formulation had a relative bioavailability of 45% and 42%, a $C_{max}$ of 99 ng/mL and 179 ng⁄mL and a $t_{max}$ of 18 and 42 minutes for the 4 mg and 7 mg doses, respectively (19).

Ivaturi *et al.* conducted a study of the bioavailability and tolerability of intranasal diazepam in healthy volunteers. They compared 5 mg and 10 mg intranasal diazepam doses of their investigational formulation with a 5 mg dose of diazepam solution intravenously. Following the 5 mg and 10 mg doses, the median $t_{max}$ were 20 and 30 minutes respectively and the mean $C_{max}$ were 134.3 ± 62 ng/mL and 247.6 ± 61 ng/mL. Estimated bioavailability was 75% for both doses. In the same study, a group of subjects was evaluated to compare 5 mg of diazepam and 5 mg of midazolam with intranasal and IV routes of administration. Intranasal diazepam was rapidly absorbed, with a $t_{max}$ of 28.8 ±20.96 minutes. $C_{max}$ was 179.2 ± 8.85 ng⁄mL and half-life was 22.4 ± 3.45 hours (20).

Results of the DIAZ.001.01 study with NRL-1 are provided above in Section 1.2.1.

Intranasal Use of Intravail in Human Subjects:

Intravail A3 is being evaluated in human clinical trials. As of September 2014, Intravail A3 has been used in: (i) eight intranasal human programs with a total of 13 human studies; and (ii) three human oral programs with a total of five human studies. These human studies have been conducted in the US and India and have included more than 280 subjects with over 3,500 aggregate doses. Each study has been a single dose study with the exception of one 7 day study with 24 subjects and one six-week study with 75 subjects. No clinically relevant AEs have been observed to date that were attributable to Intravail A3.

In three (3) completed and one ongoing clinical studies conducted outside the US with an undisclosed active pharmaceutical ingredient, 84 normal subjects have been exposed to 1 to 3 single 100 µL intranasal doses of Intravail A3 at concentrations of 0.1-0.2%. Two hundred thirty-eight (238) AEs have been reported with 237 being mild and of a nature expected with the active drug. One SAE (pancreatitis) was reported during the study, but the subject had not received the reference product containing Intravail A3.

The current toxicology and clinical studies with Intravail A3 show no evidence of any concerning or non-reversible findings at the dose levels anticipated to be used in humans.

In 2007 alkylpolyglycosides, the class of compounds, which includes Intravail A3, were the subject of a GRAS Exemption Claim submitted to the FDA (21). The subject of this claim was the use of alkylpolyglycosides as "surfactants for use in the cleaning of food products, the cleaning of equipment used to process food, the manufacture of products that come in contact with food, fruits and vegetables including meat and poultry carcasses, the cleaning of materials that subsequently come in contact with food, paper, cardboard, plastic or stainless steel lines and/or production vessels, and the cleaning and sanitizing of surfaces in food preparation areas."

In the FDA's response to the GRAS Exemption Claim (21), the FDA (Office of Food Additive Safety, Center for Food Safety and Applied Nutrition) had no questions with respect to the conclusion reached by the Applicant, stating that: "Based on the information provided by Cognis, as well as other information available to the FDA, the agency has no questions at this time regarding Cognis' conclusion that alkylpolyglycosides are GRAS under the intended conditions of use." The Agency noted that it has not, however, made its own determination regarding the GRAS status of the subject use of alkylpolyglycosides. Nonetheless, alkylpolyglycosides and Intravail A3 are commonly regarded as GRAS (22).

In September 2005, the US EPA determined that there is a reasonable certainty of no harm from aggregate exposure to residues of C10-C16-alkyl glycosides and that establishing an exemption from the requirement of a tolerance for C10-C16-alkyl glycosides will be safe for the general population including infants and children (23).

Overall the introduction of Intravail into the NRL-1 formulation is anticipated to provide an absolute bioavailability comparable to Diastat rectal gel with reduced variability and a more convenient, less invasive delivery system.

### 1.3 Study Rationale

Diazepam rectal gel (Diastat) is the only formulation of diazepam indicated for the 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, i.e., ARS.

A diazepam nasal spray is being developed for patients who experience ARS to provide an alternative more convenient and acceptable route of diazepam administration.

# 2.0 PURPOSE AND STUDY OBJECTIVES

## 2.1 Purpose

The purpose of this study is to assess the PK and safety in Epilepsy subjects under both seizure and normal conditions.

## 2.2 Study Objectives

### 2.2.1 Primary Objective

The primary objective of this study is to assess the PK of diazepam after single intranasal doses of NRL-1 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 will be the $C_{max}$ and the area under the curve through 6 hours ($AUC_{0-6}$).

### 2.2.2 Secondary Objectives

The secondary objectives of this study include:

- To compare the diazepam $C_{max}$, $t_{max}$ and $AUC_{(0-6)}$ after single administration of NRL-1 in Epilepsy subjects during the ictal or peri-ictal period to that after administration of NRL-1 to the same subjects under normal conditions;
- To compare the diazepam $C_{max}$, $t_{max}$, and $AUC_{(0-6)}$ after single administration of NRL-1 between Epilepsy subjects ages 6 to 11 and those greater than 12 years of age;
- To compare the diazepam $C_{max}$, $t_{max}$, and $AUC_{(0-6)}$ after single administration of NRL-1 in 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 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 NRL-1.

## 2.3 Description of Study Design

This is a Phase 1, open-label, PK and safety study in Epilepsy subjects under both ictal or peri-ictal (involving motor activity and/or altered awareness) and normal conditions. Two doses of intranasal NRL-1 will be administered at either 5 mg, 10 mg, 15 mg, or 20 mg based on the subject's body weight.

The study consists of a screening period, a baseline period, and a post-dose follow-up period. The NRL-1 dose will be administered during the ictal or peri-ictal period (Treatment 1) and again under normal non-seizing (intra-ictal) conditions (Treatment 2). The dosing may be done

in either order (Treatment 1 or Treatment 2 first) with approximately 14-day wash-out between doses. Follow-up telephone contacts will be conducted 7-days and 14-days after the last dose of NRL-1. Between doses of NRL-1, subjects and caregivers should avoid the use of other diazepam containing products. For subjects who will roll over to the DIAZ.001.05 long term safety study, the Day 14 (second dosing for NRL-1) assessments can be used as baseline assessments for DIAZ.001.05 to allow subjects to initiate long term treatment under the protocol.

Baseline in period 1 for this study is considered the period within 7 days of admission. The subject will be admitted and observed in the clinical site (i.e. Epilepsy Monitoring Unit [EMU] or Clinical Trial Research Center [CTRC]) and dosing will occur at the time of a seizure that is considered suitable for administration of NRL-1. All subjects will be monitored by EEG, which is considered standard of care in the EMU but part of study procedure in the CTRC, with the start and stop time of the seizure being recorded based on the EEG. Time point 0 will be defined as the time of dosing of NRL-1 and initiation of PK blood sampling. Subjects with diazepam blood levels at baseline that are equal to or greater than 10% of the $C_{max}$ will be excluded from the primary PK analysis set.

Treatment 1 with NRL-1 will initially be administered under ictal or peri-ictal conditions in a clinical setting to subjects having partial or generalized Epilepsy with motor seizures or seizures with clear alterations of awareness. Since the primary objective is to obtain diazepam plasma concentrations and PK information when the drug is given in the ictal or peri-ictal period, dosing of NRL-1 will ideally occur during or within 5 minutes after the onset of the seizure. The stop time of the seizure and any recurrence of seizure activity within the first 12 hours after dosing NRL-1 will also be recorded.

A 3 mL blood sample for PK will be collected at the baseline and at the post-dose period once admitted to the clinical site. During the post-dose period, 3 mL blood samples will be collected at predetermined times after NRL-1 dosing to determine the diazepam plasma concentration versus time profile. If the baseline pre-dose blood sample is unable to be collected, i.e., subject experiences a seizure prior to collection, then the pre-dose assessment closest to dosing will be included in the analysis.

If the subject experiences a seizure after NRL-1 dosing (during the blood sampling period), PK blood draws will be suspended as long as required for the subject's medical care and should resume when clinically feasible. Subjects may be treated with any other medication that does not contain diazepam that is standard of care. If the subject experiences a seizure after NRL-1 dosing and is administered an exclusionary medication (such as IV, oral or rectal diazepam), PK blood draws will be stopped, time of dosing diazepam recorded, and the Sponsor will be notified. All other safety procedures will be performed as per the protocol Schedule of Study Procedures (APPENDIX A).

The second treatment (Treatment 2) with NRL-1 will occur when the subject is in a normal state (intra-ictal period). Please note that it is not anticipated that subjects will be admitted to the

clinical site for Treatment 2 and the site will select an appropriate clinical facility for this portion of the study. Subjects should be seizure free for at least 12 hours prior to dosing. A 3 mL blood sample for PK will be collected at the post-dose period in the clinic prior to administration of NRL-1. During the post-dose period, 3 mL blood samples will be collected at predetermined times after NRL-1 dosing to determine the diazepam plasma concentration versus time profile.

Treatment 1 and Treatment 2 may be given in either order, provided there is at least a 14-day wash out period between doses of NRL-1 and no other diazepam containing products are used between the two NRL-1 administrations.

Safety assessments include physical and neurological examination including head, ears, eyes, nose, and throat (HEENT), vital signs, laboratories (hematology, serum chemistry, and urinalysis), 12-lead ECGs, and AE assessment. Concomitant medications will be recorded. Columbia-Suicide Severity Rating Scale (C-SSRS for adults or children), nasal irritation assessment, assessment of mucosalerythema, mucosal edema, nasal discharge, mucosal crusting and mucosal epistaxis, sedation score sssessment, and smell test (National Institutes of Health [NIH] Toolbox Odor Identification Test, (1, 2) will be conducted.

## 2.4 Study Endpoints

### 2.4.1 Primary Endpoint

The primary endpoint of this study is the PK outcome. There are no efficacy measures evaluated in this study. The PK endpoint of this trial is to determine the relative bioavailability of diazepam from NRL-1 ($C_{max}$, $t_{max}$, $AUC_{(0-6)}$) in epilepsy subjects.

### 2.4.2 Secondary Endpoints

The secondary endpoints in this study include:

- A secondary PK endpoint of this trial is to compare the diazepam $C_{max}$, $t_{max}$, and $AUC_{(0-6)}$ after single administration of NRL-1 between Epilepsy subjects ages 6 to 11 and those greater than 12 years of age in both seizure and non-seizure conditions.
- A secondary PK endpoint of this trial is to determine the relative bioavailability of diazepam from NRL-1 ($C_{max}$, $t_{max}$, $AUC_{(0-6)}$) in 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 compared to that of normal conditions and healthy normal subjects from PK data obtained in the DIAZ.001.02 and DIAZ.001.03 studies.
- Assessment of the safety events from NRL-1.
- To visually compare the $C_{max}$ and $AUC_{(0-6)}$ between the 2 age groups under seizure and non-seizure conditions.

### 2.4.3 Randomization/Assignment to Study Drug

There are no randomization/assignments to study drug as this is an open-label study.

## 2.5 Study Drugs

### 2.5.1 Test Product

NRL-1 is a solution formulation of diazepam intended for nasal administration. NRL-1 contains diazepam, Intravail A3, vitamin E, benzyl alcohol and ethanol. To provide the range of desired doses, NRL-1 will be available with three different concentrations of diazepam:

- 50 mg/mL
- 75 mg/mL
- 100 mg/mL

To obtain a 15 mg dose, two sprayers containing the 75 mg/mL formulation will be used with one 100 µL spray in each of nostril. To obtain a 20 mg dose, two sprayers containing the 100 mg/mL formulation will be used with one 100 µL spray in each of nostril.

NRL-1 is packaged in a disposable molded polymer commercially-available device marketed by Aptar Pharma as the UDS (unit dose sprayer). This single actuation device contains a small glass vial with a rubber stopper. The Aptar UDS will deliver an exact dose of 100 µL of NRL-1 solution.

### 2.5.2 Dose and Dose Justification

The dose of 5 mg, 10 mg, 15 mg, or 20 mg of NRL-1 will be selected according to the subject's weight (rounded to the nearest kg) based on the following:

For Children Age 6-11 Years:

- 10 kg to 18 kg body weight will receive a 5 mg dose (50 mg/mL, 100 µL) administered as one spray in the left nostril.
- 19 kg to 37 kg will receive a 10 mg dose (100 mg/mL, 100 µL) administered as one spray in the left nostril.
- 38 kg to 55 kg will receive a 15 mg dose (75 mg/mL, 100 µL) administered as two 7.5 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).
- 56 kg to 74 kg will receive a 20 mg dose (100 mg/mL, 100 µL) of NRL-1 administered as two 10 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).

For Age 12 Years or greater:

- 14 kg to 27 kg body weight will receive a 5 mg dose (50 mg/mL, 100 µL) administered as one spray in the left nostril.
- 28 kg to 50 kg will receive a 10 mg dose (100 mg/mL, 100 µL) administered as one spray in the left nostril.
- 51 kg to 75 kg will receive a 15 mg dose (75 mg/mL, 100 µL) administered as two 7.5 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).
- Greater than 76 kg will receive a 20 mg dose (100 mg/mL, 100 µL) of NRL-1 administered as two 10 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).

In patients, the usual dose of diazepam rectal gel (Diastat) is 0.3 mg/kg, or ~9 mg in a 30 kg child and 0.2 mg/kg or ~14 mg in a 70 kg adult. The diazepam doses selected of 5 mg to 20 mg is the low to high dose in the typical weight range for a patient. These doses are also expected to provide plasma diazepam concentrations sufficient for comparing the PK of diazepam after administration of the doses while minimizing risk to the subjects.

### 2.5.3 Pharmacokinetic Plasma Sampling

Blood samples (3 mL) will be collected in this study to measure diazepam plasma concentrations following the intranasal administration of NRL-1. All subjects will have samples collected through at least 6 hours after each of the two doses of NRL-1. Blood samples for PK will be 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 should also be obtained if feasible at 8 and 12 hours after dosing. If a blood sample collection is delayed, then the collection will occur as soon as feasible and should not be 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 samples.

The following PK parameters for diazepam will be calculated using non-compartmental analysis: $C_{max}$, $t_{max}$, $AUC_{(0-6)}$, with a concentration equal to or greater than the lower limit of quantitation.

If a second dose of NRL-1 is administered due to a subsequent seizure between 4 and 12 hours after the initial dose, when clinically feasible, PK samples should be collected based on the time of the second dose at 0 (immediately after the 2$^{nd}$ dose), 30 minutes, and 1, 2, and 4 hours after dosing.

For Treatment 1, the actual time of seizure onset, dose of NRL-1, time of seizure stop, and time of each blood sample will be recorded. PK parameters will be determined using actual times of sample collection relative to the administration of NRL-1.

### 2.5.4 Bioanalytical Method

Plasma samples will be evaluated by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method capable of detecting diazepam.

## 2.6 Concomitant Medications

### 2.6.1 Prior and Concomitant Medications

Prior medications are defined as medications that were taken within 30 days prior to initial dosing with study drug.

Concomitant medications are defined as medications taken any time after the start of dosing until the discharge at the end of the Treatment period 2.

The use of over-the-counter (OTC) oral and/or nasal decongestants is not permitted for the 7 days prior to the screening period or during the study. Other OTC medications are not allowed within seven (7) days of the first dose. All prescription medications are not allowed within fourteen (14) days of the first dose of NRL-1.

### 2.6.2 Restricted Concomitant Medications

Treatment with any known strong or moderate inhibitors or inducers of metabolizing enzymes (e.g., CYP-P450 enzymes or MAO) within fourteen (14) days prior to the first dose of NRL-1, or during the study, is prohibited without approval from the Medical Monitor (See APPENDIX E for list of prohibited medications).

Use of OTC oral and/or nasal decongestants within 7 days prior to the first dose of study drug or during the study.

Treatment with any other diazepam containing product within 14 days prior to the first dose of study drug or during the study.

## 2.7 Procedures for Monitoring Subject Compliance

Subjects will be in the clinical trial site for the dosing and blood sampling portion of the trial. Between dosing periods, subjects will be allowed to return home. Subjects will return to the clinic for subsequent dosing periods and for clinical assessments.

# 3.0 STUDY POPULATION

The study population will be subjects with a clinical diagnosis of epilepsy who, in the opinion of the Investigator, may need a benzodiazepine for seizure control.

## 3.1 Inclusion Criteria

For a subject to be eligible for this study, s/he must meet **ALL** of the following criteria:

1. Male and female subjects between the ages of 6 and 65 years, inclusive.
2. Written informed consent to participate in the study.
3. Body mass index (BMI) not to exceed 35 kg/m², inclusive.
4. Subject has a clinical diagnosis of Epilepsy and, in the opinion of the Investigator, may need benzodiazepine intervention for seizure control.
5. Subjects having either partial or generalized Epilepsy with motor seizures or seizures with clear alteration of awareness are eligible for enrollment.
6. Female subjects of childbearing potential, defined as having a menstrual cycle and who are not surgically sterile or less than two (2) years postmenopausal, must complete a pregnancy screen and agree to utilize one of the following forms of contraception during the study and for 21 days after the last dose of study drug: abstinence, hormonal (oral, transdermal, implant, or injection), barrier (condom, diaphragm with spermicide), intrauterine device (IUD), or vasectomized partner (six months minimum).
7. No clinically significant abnormal findings in the medical history, on the physical examination, ECG (corrected QT interval [QTcF] < 450 msec for males and QTcF < 470 msec for females), or clinical laboratory results during screening.
8. Subjects and caregivers must agree to return to the study site for all study visits and must be willing to comply with all required study procedures.

## 3.2 Exclusion Criteria

Subjects must **NOT** meet any of the following Exclusion criteria to be eligible for enrollment:

1. Subject is undergoing intracranial EEG monitoring.
2. A history of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, severe seasonal or non-seasonal allergies, nasal polyps or any nasal passage abnormality that could interfere with nasal spray administration, or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results.

3. Subject has had significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening.
4. Subjects with active major depression or a past suicide attempt documented on the Baseline/Screening C-SSRS. The children C-SSRS should be used for subjects age 6 to 11. The adult C-SSRS should be used for subjects 12 and greater years of age.
5. Any Suicidal Ideation of 3, 4, or 5 or any Suicidal Behavior in Lifetime using C-SSRS.
6. A history of allergic or adverse responses to diazepam or any comparable or similar product.
7. Subjects who (for whatever reason) have been on an abnormal diet (such as one that severely restricts specific basic food groups [e.g., ketogenic diet], limits calories [e.g., fast], and/or requires the use of daily supplements as a substitute for the foods typically eaten at mealtimes), during the four (4) weeks preceding the study.
8. Subjects who donated blood or plasma within 30 days of the first dose of study drug.
9. Participation in a clinical trial within 30 days prior to the first dose of study drug. Participation in an observational (non-interventional) study is not excluded as long as there are no scheduling conflicts with this study.
10. Inadequate or difficult venous access that may jeopardize the quality or timing of the PK samples.
11. Female subjects who are trying to conceive, are pregnant, or are lactating.
12. Positive serum pregnancy (ß-hCG) test at screening or urine pregnancy test prior to each administration of study drug for all women of childbearing potential.
13. Positive blood screen on subjects age 12 or greater for human immunodeficiency virus (HIV), Hepatitis B surface antigen (HbSAg), or Hepatitis C, or a positive urine screen for alcohol, or drugs of abuse, or cotinine. When marijuana was used for medical reasons in the opinion of the investigator, it is not considered as drug abuse and the patient can be enrolled even if the marijuana metabolites in the urine revealed as positive.
14. Treatment with phenobarbital or primidone within 30 days of the anticipated dosing visit (i.e., baseline).
15. Treatment with warfarin or dabigatran or other blood thinners within 30 days of the anticipated dosing visit (i.e., baseline).
16. Treatment with any diazepam containing products within 14 days of the anticipated dosing visit (i.e. baseline).
17. Use of nasal decongestants or nasal steroids within 7 days prior to the screening visit or during the study.
18. Subject does not have the flu, rhinitis or any other nasal condition that would impact absorption of intranasal diazepam.

### 3.3 Other Restrictions

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Treatment with any known strong or moderate inhibitors or inducers of metabolizing enzymes (e.g., CYP-P450 enzymes or MAO) within fourteen (14) days prior to the first dose of NRL-1, or during the study, is prohibited without approval from the Medical Monitor (See APPENDIX E for list of prohibited medications).
2. Use of OTC oral and/or nasal decongestants for the 7 days prior to the first dose of study drug or during the study.
3. Smoking and the use of tobacco products in excess of 10 cigarettes or 1 cigar per day is not permitted for one (1) month prior to the first dose of Study Drug and for the duration of the study. When marijuana was used for medical reasons in the opinion of the investigator, it is not considered as drug abuse and the patient can be enrolled even if the marijuana metabolites in the urine revealed as positive.
4. Subjects should not engage in strenuous exercise during the confinement period of the study.

## 4.0 SAFETY ASSESSMENTS

### 4.1 Collection of Adverse Events Data

Data regarding TEAEs will be collected in this study. TEAEs are events that are not present at baseline, or if present at baseline, have worsened in severity. AEs will be assessed during the blood sampling period and until follow-up phone calls.

Any AE reported by the subject or noted by the Investigator or his/her designee will be recorded on the case report form (CRF) regardless of the Investigator opinion of causality. The following information will be recorded for each AE: description of the event, date and time of onset, date and time of resolution, severity, causal relationship to study drug, outcome, action taken with the study drug and any treatment given.

All clinically significant abnormal changes from baseline in physical examination findings, vital signs, ECGs, and laboratory evaluations will be collected, graded with regards to severity or clinical significance, assessed for causal relationship and recorded on the CRF.

### 4.2 Clinical Laboratory Evaluations

Screening blood samples and urine specimens for laboratory evaluation may be collected up to 21 days prior to initial dose of study drug.

Baseline blood and urine samples in period 1 must be collected within 7 days of admission to the clinical site. Results must be evaluated prior to dosing. If an abnormal test result of clinical significance is obtained at baseline that was not clinically significant at screening, the test will be repeated within 7 days and dosing will be delayed until the value is no longer clinically significant.

Subjects with clinically significant abnormal laboratory values during the study will be monitored until the value is no longer considered clinically significant or no further change is anticipated. All abnormal changes from baseline in laboratory values will be collected, graded with regards to severity, assessed with regards to causality and recorded in the CRF to be reported as abnormal laboratory findings. Only clinically significant abnormal laboratory findings associated with clinical sequelae or that require therapeutic intervention are considered AEs. All clinical laboratory analyses will be performed at the clinical site and the results will be recorded on the appropriate CRF. Clinical laboratory reports must be reviewed, signed, and dated by the Investigator. The Investigator will assess each abnormal test result for clinical significance and the result of the evaluation will be recorded on the CRF.

### 4.2.1 Hematology

Complete blood cell count (CBC) will include red blood cell (RBC), RBC morphology, reticulocyte count, hemoglobin, hematocrit, white blood cell (WBC) with differential, and platelet count.

### 4.2.2 Serum Chemistry

Comprehensive metabolic panel will include serum alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, calcium, phosphorus, chloride, sodium, potassium, blood urea nitrogen (BUN), creatinine, total bilirubin, albumin, total protein, amylase, bicarbonate/carbon dioxide ($CO_2$), uric acid, and lactate dehydrogenase (LDH).

### 4.2.3 Urinalysis

Urinalysis will include appearance, color, pH, specific gravity, glucose, protein, ketones, blood, creatinine clearance, and a detailed microscopic analysis. Microscopic analysis will be performed regardless of macroscopic results and will include the following: WBC, RBC, cast/type, crystal/type, and bacteria. Standard urinalysis will be conducted on the same day as blood chemistry.

### 4.2.4 Urine Drug and Alcohol Screen

Urine samples will be collected at screening and baseline for amphetamines, barbiturates, cocaine metabolites, methadone, opiate metabolites, phencyclidine, marijuana metabolites, and alcohol. When marijuana used for medical reasons in the opinion of the invesigator, it is not

considered a drug abuse and the patient can be enrolled even if the marijuana metabolites in the urine revealed as positive. In this case, information about marijuana use for medical reasons should be entered in the CRF page as a concomitant medication.

### 4.2.5 Other Blood Tests

The presence of HIV antibody, HbSAg, and Hepatitis C antibody will be assessed at screening.

## 4.3 Physical Examinations and Medical History

### 4.3.1 Physical and Neurological Examinations

The Investigator or designee will perform a physical and neurological examination at screening and baseline. Results will be recorded on the appropriate page of the CRF.

### 4.3.2 Medical History

A medical history including seizure history will be obtained at screening and baseline. Medical history will include demographic data (age, sex, race/ethnicity, etc.). The C-SSRS, a measure of suicidal ideation and behavior, will be used to document suicidality at screening, baseline, and at 6 hours post dose in order to classify suicidal events using the Columbia Classification Algorithm of Suicide Assessment. The children C-SSRS should be used for subjects age 6 to 11. The adult C-SSRS should be used for subjects 12 and greater years of age.

## 4.4 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS, a measure of suicidal ideation and behavior, will be used to document suicidality in order to classify suicidal events. Suicidality will be accessed at screening and baseline (pre-dose) and post-dosing at 6 hours. For adults, screening and baseline assessments will use the Baseline/Screening Phase 1 version of the C-SSRS. The Since Last Visit version of the C-SSRS will be used for post-dosing assessments. For children, screening and baseline assessments will use Children's Baseline/Screening and Children's Since Last Visit will be used for post-dosing assessments (APPENDIX C)

## 4.5 ECG

A standard supine (after resting for at least 5 minutes) 12-lead ECG will be performed in triplicate by a trained technician at screening and baseline visits.

ECGs will be assessed by the Investigator or a cardiologist, and a comparison to baseline ECGs will be performed. The ECG report must be reviewed, signed, and dated by the Investigator or cardiologist. One duplicate copy of the ECG tracing and the evaluation report will be printed and sent to the Sponsor after de-identifying the subject for inclusion with the CRF. The original ECG results will be kept on file at the site as source documentation.

### 4.6 Height and Weight

Height will be measured in centimeters at screening. Body weight will be measured in kilograms at screening and baseline. Height and weight will be recorded on the CRF.

### 4.7 EEG

Subjects will be monitored for seizure activity with a continuous EEG evaluation. The EEG is considered standard of care when in the EMU setting, but is part of the study procedure if in CTRC setting. The start time, stop time, and type of seizure will be recorded based on the EEG results. The time of NRL-1 dosing will also be recorded as part of the study database.

### 4.8 Vital Signs

Vital signs (temperature, pulse, respiration rate and blood pressure) are to be obtained at screening, baseline, and at 45 (± 5 min) minutes, 2 (± 15 min), 4 (± 30 min), 6 (± 30 min), 8 (± 30 min), and 12 (± 30 min) post dosing and at discharge. Vital signs at 8 (± 30 min) and 12 (± 30 min) hours are optional. Vital signs will be recorded on the CRF.

### 4.9 Smell Test

Smell tests will be conducted at baseline, at 1 hour (± 15 min), 4 hours (± 30 min) post dosing, and at discharge. The NIH Toolbox Odor Identification Test will be used as smell tests (1, 2).

### 4.10 Nasal Irritation Assessments

Objective evaluations of nasal irritation will be assessed by a trained observer after administration of the intranasal formulation. Nasal irritation will also be evaluated prior to each administration of NRL-1 (baseline) and at 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge. Mucosal erythema, mucosal edema, nasal discharge, mucosal crusting and mucosal epistaxis will be evaluated on separate scales prior to each dose of NRL-1 (baseline), and at 30 (± 10 min) minutes, and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge. The subjects will also be required to report any incident of nasal irritation or mucosal epistaxis in-between evaluation time points and during follow up contacts. See Section 12.4 for assessment scales.

### 4.11 Pregnancy Test

A serum ß-hCG will be administered to females of childbearing potential at screening. Urine pregnancy test is only required for female subjects of child bearing potential. A urine pregnancy test will be conducted at baseline prior to each treatment with NRL-1. Please note that subjects age 6 to 11 are not required to take a pregnancy test.

If a pregnancy occurs in the subject or in the partner of a subject during the course of the study, the Investigator must report it to the Sponsor within 24 hours using the pregnancy notification

form provided by the sponsor. For females who experience pregnancy during the trial, the study medication will be discontinued immediately and the patient will be monitored for any adverse problems with the pregnancy.

## 5.0 PHARMACOKINETICS

The following PK parameters for diazepam will be calculated using non-compartmental analysis: $C_{max}$, $t_{max}$, and $AUC_{(0-6)}$. Blood samples (3 mL) will be collected in this study to measure diazepam plasma concentrations following the intranasal administration of NRL-1. All subjects will have samples collected through at least 6 hours after each of the two doses of NRL-1. Blood samples for PK will be 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 should also be obtained if feasible at 8 and 12 hours after dosing. If a blood sample collection is delayed, then the collection will occur as soon as feasible and should not be 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 samples.

For subjects that have blood samples collected beyond 6 hours, the area under the diazepam plasma concentration versus time curve through the last sample ($AUC_t$) will be calculated. For subjects that have blood samples collected through 12 hours, the area under the diazepam plasma concentration versus time curve through 12 hours ($AUC_{12h}$) will be calculated.

If a second dose of NRL-1 is administered due to a subsequent seizure between 4 and 12 hours after the initial dose, when clinically feasible, PK samples should be collected based on the time of the second dose at 0 (immediately after the 2$^{nd}$ dose), 30 minutes, and 1, 2, and 4 hours after dosing.

For Treatment 1, the actual time of seizure onset, dose of NRL-1, time of seizure stop, and time of each blood sample will be recorded. PK parameters will be determined using actual times of sample collection relative to the administration of NRL-1.

## 6.0 PHARMACODYNAMICS

No pharmacodynamic measures will be assessed during this trial.

## 7.0 EFFICACY

No efficacy measures will be assessed during this study.

# 8.0 STUDY VISITS

Refer to APPENDIX A for the Schedule of Study Procedures.

Within a period of 21 days before dosing, all screening tests establishing subject eligibility will be performed.

In addition to signing the Informed Consent Form (ICF) and meeting the protocol-specified entrance criteria, eligible subjects must agree to return to the study site for all study visits, including the confinement period during each treatment. The study schedule will be provided in writing for the subject's review and signature acknowledging agreement.

## 8.1 Screening

The Investigator or his/her approved designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign the ICF. Written informed consent must be provided by the potential study participant prior to initiation of any screening evaluations or other study-related procedures. The signature date and the name of the individual at the site who obtained the informed consent will be recorded in the subject's medical record.

After written informed consent is obtained, the subject will be assigned a screening number and will undergo the designated screening procedures listed in APPENDIX A within 21 days prior to study drug administration. The Investigator will assess the results of these screening evaluations to determine eligibility for entry into the study according to the inclusion/exclusion criteria listed in Section 3.0.

## 8.2 Screening Evaluations (Days -21 to -1)

After subjects have signed an Institutional Review Board/Ethics Committee (IRB/EC) approved ICF for the purpose of this study, they will begin the screening process. Screening evaluations may be performed up to 21 days in advance of dosing, but must be completed at least one (1) day prior to dosing.

- The following study evaluations and procedures are required to determine eligibility: Medical history including seizure history, demographics, prior medications, and concomitant medications.
- The C-SSRS, a measure of suicidal ideation and behavior, will be used to document suicidality at screening, baseline, and post-dosing at 6 hours. The children C-SSRS should be used for subjects age 6 to 11. The adult C-SSRS should be used for subjects 12 and greater years of age. The screening assessment will use the Baseline/Screening Phase 1 version of the C-SSRS. If the subject has active major depression or a past suicide attempt, she/he is not eligible for the study.

- Physical and neurological examination, including height (at screening only) and weight measurements.
- Vital signs consisting of temperature, pulse, and blood pressure.
- Blood and serum samples for the following laboratory evaluations:
    - Hematology
    - Serum chemistry
    - Serum ß-hCG (all females)
    - HIV antibody
    - Hepatitis screening
- Urinalysis
- Urine drug and alcohol test
- 12-lead ECG (in triplicate)

### 8.3 Baseline Evaluations (Day -7 to 0, pre-dose period 2)

Following the screening visit, subjects determined to be eligible for participation in the study will undergo baseline assessments after admission to the clinical site and within 7 days prior to dosing in period 1 and 48 hours for period 2.

Baseline assessments include the following:

- Any restricted concomitant medications
- Medical history (at baseline period 1 only)
- Physical and neurological examinations including weight
- Vital signs consisting of temperature, pulse, respiratory rate and blood pressure.
- Blood and serum samples for the following laboratory evaluations:
    - Hematology
    - Serum chemistry
    - PK
- Urine samples
    - Urine pregnancy test
    - Urine drug and alcohol screen
    - Urinalysis
- 12-lead ECGs

- Smell Test (1, 2)
- C-SSRS. The children C-SSRS should be used for subjects age 6 to 11. The adult C-SSRS should be used for subjects 12 and greater years of age
- Nasal examination and irritation assessments (The following will be assessed on separate scales: nasal irritation, erythema, edema, nasal discharge, mucosal erythema, mucosal edema, nasal discharge, mucosal crusting and mucosal epistaxis)
- Sedation score assessment
- Visual analog scale (VAS)
- EEG Monitoring (continuous)

## 8.4 Drug Administration

Treatment 1 with NRL-1 will be administered under ictal or peri-ictal conditions in a clinical setting to subjects having partial or generalized Epilepsy with motor seizures or seizures with clear alterations of awareness. Since the primary objective is to obtain diazepam plasma concentrations and PK information when drug is administered in the ictal or peri-ictal period, dosing of NRL-1 will occur within 5 minutes after the onset of the seizure. The stop time of the seizure and any recurrence of seizure activity within the first 12 hours after dosing NRL-1 will also be recorded.

The second treatment (Treatment 2) with NRL-1 will occur when the subject is in a normal state (intra-ictal period). Please note that it is not anticipated that subjects will be admitted to the clinical site for Treatment 2 dosing and the site will select an appropriate clinical facility for this portion of the study. Subjects should be seizure free for at least 12 hours prior to dosing. A 3 mL blood sample for PK will be collected at the post-dose period in the clinic prior to administration of NRL-1. During the post-dose period, 3 mL blood samples will be collected at predetermined times after NRL-1 dosing to determine the diazepam plasma concentration versus time profile.

Treatment 1 and Treatment 2 may be given in either order, provided there is at least a 14-day wash out period between doses of NRL-1 and no other diazepam containing products are used between the two NRL-1 administrations.

Study site personnel are responsible for administering all study drugs. The calendar date and 24-hour clock time of all doses will be recorded on the CRF.

## 8.5 Collection of Blood Samples

Blood samples (3 mL) for the measurement of plasma concentrations of diazepam will be collected in blood collection tubes (e.g.,Vacutainers®) containing $K_2$-ethylenediaminetetraacetic acid (EDTA) [1 x 6 mL].

All subjects will have 3 mL samples collected through at least 6 hours after each of the two doses of NRL-1. If clinically feasible, additional samples will be collected through 12 hours post-dose. Blood samples for PK will be obtained at Baseline upon admission to the clinical site (EMU or CTRC) for each treatment, Pre-dose (prior to each treatment of NRL-1), and at 15, 30, and 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. Blood samples at 8 (± 30 min) and 12 (± 30 min) hours are optional. If a blood sample collection is delayed, then the collection will occur as soon as feasible and should not be 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.

If a second dose of NRL-1 is administered due to a subsequent seizure between 4 and 12 hours after the initial dose, when clinically feasible, PK samples should be collected based on the time of the second dose at 0 (immediately after the 2$^{nd}$ dose), 30 minutes, and 1, 2, and 4 hours after dosing.

The calendar date and 24-hour clock time of all blood samples will be recorded on the CRF.

Blood samples will be stored on ice prior to processing, which will begin within 60 minutes of collection. Plasma will be separated by centrifugation (e.g., 3000 rpm x 10 minutes at 0°C to approximately 4°C) and equal aliquots transferred to two (2) clearly labeled tubes and stored in a freezer at approximately -20°C. Temperature excursions will be allowed as per the current standard operating procedure (SOP) at the clinic or laboratory.

Samples will be packed in Styrofoam shipping containers with a sufficient amount of dry ice to maintain frozen conditions for at least 72 hours (3 days).

One aliquot of each sample will be sent by courier to:

inVentive Health Clinique, Inc.
Attn: Sample Coordinator
2500 Einstein Street
Quebec, Canada GIP 0A2

Telephone: 418-688-5212
Fax: 1-858-436-1401

The remaining aliquots will be sent to the analytical laboratory after the site receives written confirmation that the originals have been received and inventoried.

## 8.6 Day 0 (post-dose) up to Discharge

Post-dose assessments include the following (Refer Appendix A1 and A2 for the timing of each assessment):

- Vital signs consisting of temperature, pulse, respiratory rate and blood pressure
- Blood samples for PK
- C-SSRS. The children C-SSRS should be used for subjects age 6 to 11. The adult C-SSRS should be used for subjects 12 and greater years of age
- Nasal examination and irritation assessments (The following will be assessed on separate scales: nasal irritation, erythema, edema, nasal discharge, mucosal erythema, mucosal edema, nasal discharge, mucosal crusting and mucosal epistaxis)
- Sedation score assessment
- Smell Test (1)
- VAS
- Concomitant medications
- AEs

There will be at least a 14 day wash-out period between the treatments (if subjects are on oral contraceptives (OC) the period between dosing should be extended to approximately 28-days to ensure that the subject is dosed at the same approximate time of the OC cycle). Subjects may discharge from the clinic after blood sample at 6 hours (or optional 8 and 12 hours) post dose is complete followed by the discharge assessments. When discharge occurs after 6 hours post dose, the assessments at discharge that overlap with the assessments at 6 hours post dose do not have to be repeated.

Treatment 1 and Treatment 2 may be given in either order, provided there is at least a 14-day wash out period between doses of NRL-1 and no other diazepam containing products have been used between the two NRL-1 administrations.

For subjects who will roll over to the DIAZ.001.05 long term safety study, the Day 14 (second dosing day for NRL-1) assessments can be used as baseline assessments for DIAZ.001.05 to allow subjects to initiate long term treatment under that protocol.

## 8.7 Follow-up Telephone Contact

Follow-up phone calls 7 days (± 2 days) and 14 days (± 3 days) will be conducted after the last dose of NRL-1 to determine if any AE has occurred and to follow-up on any TEAEs ongoing since last communication with the subject.

### 8.8 Termination Procedures

At early termination, all subjects will be contacted by phone calls approximately 7 days (± 2 days) after the final dose of NRL-1.

## 9.0 PREMATURE DISCONTINUATION FROM STUDY

A premature discontinuation from study will occur when a subject who signed informed consent ceases participation in this study, regardless of circumstances, prior to completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- Failure to meet inclusion/exclusion criteria before receiving first dose of study drug has been administered
- Female subjects who experienced pregnancy
- Death
- Significant safety event that in the opinion of the Investigator warrants discontinuation
- Lost to follow-up after every attempt has been made to contact the subject, including sending a registered letter
- Subject withdraws consent

The Principal Investigator (PI) and the IRB/EC reserve the right to prematurely terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to prematurely terminate the study at any time for administrative reasons.

Subjects will be followed for one-week after the administration of the last dose of study drug for early termination (Termination Procedures).

## 10.0 PRODUCT SPECIFICATIONS

### 10.1 Description

Diazepam, illustrated in Figure 1, is a benzodiazepine anticonvulsant with the chemical name; 7-chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one. It is a colorless to light yellow crystalline compound, insoluble in water. The empirical formula is $C_{16}H_{13}ClN_2O$ and the molecular weight is 284.75.

NRL-1 is a solution formulation of diazepam intended for nasal administration. NRL-1 contains diazepam, Intravail A3, vitamin E, benzyl alcohol and ethanol. To provide the range of desired doses, NRL-1 will be available with four different concentrations of diazepam;

- 50 mg/mL (5 mg)
- 100 mg/mL (10 mg)
- 75 mg/mL (15 mg administered as two 7.5 mg sprays)
- 100 mg/mL (20 mg administered as two 10 mg sprays with one in each nostril)

The drug product is manufactured under current Good Manufacturing Practices (cGMP) at a contract manufacturing facility.

### 10.2 Formulation, Packaging, and Labeling

NRL-1 will be supplied for this study as either the 50 mg/mL, 75 mg/mL, or 100 mg/mL formulation planned for commercial distribution.

NRL-1 is packaged in a disposable molded polymer commercially-available device marketed by Aptar Pharma as the UDS. This single actuation device contains a small glass vial with a rubber stopper. The Aptar UDS will deliver an exact dose of 100 µL of NRL-1 solution.

Each vial of NRL-1 study drug packaging will be affixed with a single label panel containing the following information:

> NRL-1 (Intranasal Diazepam)
> 50, 75 or 100 mg/mL (w/v) each vial to deliver 100 µL
> Lot: XXXXX

### 10.3 Receipt, Storage and Stability of NRL-1

NRL-1 will be packaged in a glass vial with the commercially available UDS and placed in boxes. Excursions are permitted to 15- 30 °C (59˚F to 86 ˚F), and after receipt should be stored at 15 - 25 °C (59 ˚F-77˚F) [see USP Controlled Room Temperature] until use.

### 10.4 Preparation of Study Drug

NRL-1 is supplied as a solution for intranasal administration. Dosing is based on the cohort assignment. There is no manipulation or preparation of study drug required. NRL-1 will be dispensed to study staff responsible for administration to study subjects and reconciliation will occur after dosing.

### 10.5 Administration of Study Drug

Study drug shall be administered in the clinical site on days where subjects will be held for PK evaluations. The dose of 5 mg, 10 mg, 15 mg, or 20 mg of NRL-1 will be selected according to the subject's weight (rounded to the nearest kg) based on the following:

For Children Age 6-11 Years:

- 10 kg to 18 kg body weight will receive a 5 mg dose (50 mg/mL, 100 µL) administered as one spray in the left nostril.
- 19 kg to 37 kg will receive a 10 mg dose (100 mg/mL, 100 µL) administered as one spray in the left nostril.
- 38 kg to 55 kg will receive a 15 mg dose (75 mg/mL, 100 µL) administered as two 7.5 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).
- 56 kg to 74 kg will receive a 20 mg dose (100 mg/mL, 100 µL) of NRL-1 administered as two 10 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).

For Age 12 Years or greater:

- 14 kg to 27 kg body weight will receive a 5 mg dose (50 mg/mL, 100 µL) administered as one spray in the left nostril.
- 28 kg to 50 kg will receive a 10 mg dose (100 mg/mL, 100 µL) administered as one spray in the left nostril.
- 51 kg to 75 kg will receive a 15 mg dose (75 mg/mL, 100 µL) administered as two 7.5 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).
- Greater than 76 kg will receive a 20 mg dose (100 mg/mL, 100 µL) of NRL-1 administered as two 10 mg sprays with one in each nostril (the left nostril will be sprayed first followed by the right nostril).

### 10.6 Ordering and Distribution of Study Drug

Please contact your Clinical Research Associate or Study Project Manager to order clinical supplies.

### 10.7 Accountability of Study Drugs

All study drugs received, dispensed, and returned must be accounted for in the study drug Dispensing Log, including:

- Subject number and initials
- Date study drug was dispensed
- Quantity of study drug dispensed
- Quantity of study drug returned

All study drug received and dispensed by the Investigator will be inventoried and accounted for throughout the study. The study drug must be stored in a restricted area with limited access. Contents of the study drug containers must not be combined.

The Investigator must maintain an accurate, up to date Dispensing Log for all study drugs supplied by the Sponsor. Study drug dispensed for all subjects must be recorded on the Drug Accountability Form. The study drug Dispensing Log and remaining drug inventory will be reviewed at each monitoring visit by the Sponsor-designated clinical monitor.

The study drug supplied for this study is for use only in subjects properly consented and enrolled into this protocol. Study drugs must be kept in a secure location physically separated from standard clinic or office drug supplies.

## 11.0 SAFETY MONITORING AND ADVERSE EVENTS

### 11.1 Adverse Events

Data regarding TEAEs will be collected in this study. TEAEs are events that are not present at baseline, or if present at baseline, have worsened in severity.

**Definition of Adverse Events and Adverse Drug Reactions:**

AEs in the CRF will be classified according to the most recent FDA definitions and in a manner consistent with International Conference on Harmonization (ICH) guidelines. As such the following definitions will be used:

An AE is 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 attribution. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (e.g., worsening of asthma). A laboratory abnormality will be reported on the "Adverse Event" case report form only if it is associated with clinical sequelae or requires therapeutic intervention. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.

The reporting period for non-serious AEs starts after the first administration of study drug on Day 0 and ends at telephone contact on Day 28.

If an AE remains unresolved at the telephone contact on Day 28, the subject will be followed, at the Investigator's discretion, until resolution of the event. SAEs must be followed until resolution by the PI, even if this extends beyond the study-reporting period. Resolution is

defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

The Investigator will assess AEs for severity, relationship to IP, and as to whether the event meets one or more of the definitions of an SAE. The assessments will be recorded on the source documents and AE CRF, using the categories defined below.

| Causality Category | Description |
|---|---|
| Unlikely | A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. For the purpose of this protocol, the term unlikely will be considered not related to study medication and an "Adverse Event". |
| Possible | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. For the purpose of this protocol, an event that has possible relationship to study medication will be defined as a "Suspected Adverse Drug Reaction". |
| Probable | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. For the purpose of this protocol, an event that has probable relationship to study medication will be defined as an "Adverse Drug Reaction". |

In order to classify adverse events and diseases, preferred terms will be assigned by the sponsor or its designee to the original terms entered on the CRF, using MedDRA.

For those AEs that are not described on the CTCAE v 4.0, such AEs will be graded on a 5-point scale (mild, moderate, severe) and reported as indicated on the CRF. Intensity of such an AE is defined as follows:

**Table 3: Severity Assessment Terminology for Reporting Adverse Events (CTCAE v 4.03)**

| CTCAE Grade | Common Term | Description |
|---|---|---|
| 1 | Mild | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |

| CTCAE Grade | Common Term | Description |
|---|---|---|
| 2 | Moderate | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. |
| 3 | Severe | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. |
| 4 | Life-Threatening | Life-threatening consequences; urgent intervention indicated. |
| 5 | Death | Death related to AE |

## 11.2 Serious Adverse Events

According to the ICH Guidelines for Good Clinical Practice (E6), an SAE is any untoward medical occurrence during the course of a clinical investigation 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

Although not an SAE, exposure to study drug during pregnancy, even if no AE is reported in the mother, should be reported within 24 hours.

### 11.2.1 Reporting Requirements for Serious Adverse Events

All SAEs must be reported to the Sponsor by the Investigator, study coordinator, other designated study personnel, or clinical research associate within 24 hours of notification of the SAE. To report such events, an SAE form must be completed by the Investigator and sent within 24 hours by email or fax with relevant information.

Within the 48 hours following the initial report, the Investigator must provide further information on the SAE. This should include a copy of the completed SAE form, and any other information that will assist the understanding of the event. Significant new information on ongoing SAEs should be provided promptly as a follow-up.

The Investigator also must report all SAEs promptly to the appropriate IRB/EC as required by the institution.

**Report SAEs by fax or email to:**
**Fax: +1-858-769-0288**
**Email: NeurelisSafety@pacificlinkconsulting.com**

**Table 4: Contact Information for SAE Reporting**

| **Primary Contact** | | **Sponsor Contact** | |
|---|---|---|---|
| **Medical Monitor** | | **Clinical Manager:** | |
| **Sarina Tanimoto, MD, PhD** | | **Robert Hasson** | |
| Mobile: | 1-858-774-8716 | Mobile: | 1-619-540-6253 |
| Office: | 1-858-227-3008 | Office: | 1-858-368-9925 |
| Fax: | 1-858-436-1401 | Fax: | 1-858-436-1401 |
| Email: | sarina@pacificlinkconsulting.com | Email: | rhasson@pacificlinkconsulting.com |

### 11.2.2 Recording of Serious Adverse Events

All SAE information must be recorded on the SAE form provided by the Sponsor. Additional follow-up information (e.g., test results, autopsy, and discharge summary) must be obtained to supplement the SAE report form. A copy of all initial and follow-up reports must be filed with the subject's CRF.

## 12.0 STATISTICAL CONSIDERATIONS

### 12.1 Sample Size Determination

Approximately forty-five (45), male and female subjects, 15 subjects age 6 to 11 years and 30 subjects over 12 years of age, are to be enrolled as part of this study with dosing during the ictal or peri-ictal period of a seizure. Of these, at least 10 adult subjects and 5 pediatric subjects will have PK assessments after dosing during the ictal period.

Individual subject plasma concentrations, actual sampling times, and PK parameters will be listed by analyte and treatment. Descriptive statistics will be calculated by analyte, age group (6 to 11 years being one group and those over 12 years of age being the other group) and treatment for plasma concentrations and PK parameters. Additional exploratory analyses will be 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 will be displayed on linear and semi-logarithmic axes.

A separate but identical analysis will be performed on the observed PK parameters depending on which age group the subject belongs. The PK parameters $C_{max}$ and $AUC_{(0-6)}$ for diazepam will be compared for the first dose of NRL-1 under seizing conditions to the second dose of NRL-1 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. $C_{max}$ and $AUC_{(0-6)}$ will be normalized to the 10 mg dose prior to analysis. Confidence intervals (CI) (90%) will be constructed for the geometric mean ratio (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 will be exponentiated back to the original scale. Dose equivalence will be concluded if the 90% CI for the GMRs among the two comparisons of the two parameters fall within 80% to 125%.

For $AUC_{0-6}$ and $C_{max}$, the geometric mean (inverse log-transformed) and the 90% CI for geometric means will be compared to those observed in DIAZ.001.02 and DIAZ.001.03.

The $C_{max}$ and $AUC_{0-6}$ determined in epilepsy subjects in the ictal and peri-ictal period will be compared between the same subject in a normative state. The $C_{max}$, $t_{max}$, and $AUC_{0-6}$ determined in epilepsy subjects will also be compared to those results in healthy, non-seizing, volunteers.

The $C_{max}$ and $AUC_{(0-6)}$ will be visual compared between the two age groups in both seizure/non-seizure conditions.

The number of subjects is based on the results of Study DIAZ.001.01 in which the coefficient of variation for natural log-transformed $C_{max}$ for diazepam (excluding the IV treatment) was 38%. $C_{max}$ was the parameter with the greatest variability. Assuming half of this value is a result of the intra-subject variability (%CV = 19%), approximately 27 subjects would be required per age group. The sample size assumes 80% power to obtain 90% CI for the GMR within 80% and 125% with $\alpha = 0.05$, and a true mean treatment ratio ($\mu_T/\mu_r$) = 0.95. Given the nature of this study population, up to 45 subjects will be enrolled to obtain at least 30 evaluable subjects who complete both PK sampling periods of the study.

### 12.2 Analysis Data Sets

Subjects who receive at least one dose of NRL-1 will be included in the safety analyses. Subjects who complete the study through the 6 hours PK sampling periods on at least one of the dosing days will be included in the primary PK analysis and preliminary efficacy assessment. For the comparative bioavailability assessment, plasma samples from all subjects that complete the two periods of the study will be analyzed.

### 12.3 Pharmacokinetic Data Analyses

The following PK parameters for diazepam will be calculated using non-compartmental analysis: $C_{max}$, $t_{max}$, and $AUC_{(0-6)}$ with a concentration equal to or greater than the lower limit of quantitation.

If a second dose of NRL-1 is administered due to a subsequent seizure between 4 and 12 hours after the initial dose, when clinically feasible, PK samples should be 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 NRL-1, time of seizure stop, and time of each blood sample will be recorded. PK parameters will be determined using actual times of sample collection relative to the administration of NRL-1.

Individual subject plasma concentrations, actual sampling times, and PK parameters will be listed by analyte and treatment. Any plasma concentration below the limit of quantitation (BLQ) will be reported as zero prior to $t_{max}$ and as "BLQ" after $t_{max}$, which essentially treats it as a missing value.

Descriptive statistics will be calculated by analyte and treatment for plasma concentrations and PK parameters. Individual subject and mean plasma concentrations will be displayed on linear and semi-logarithmic axes.

## 12.4 Safety

Safety data will be summarized by dose group and based on their initial dose level or treatment group (i.e. if a dose reduction occurs they will be considered in their initial group). Descriptive statistics will be provided for actual values and change from baseline values for physical and neurological examination including HEENT, vital signs, clinical laboratory tests (serum chemistry, hematology, and urinalysis), and C-SSRS assessments (children and adult).

A nasal examination and irritation assessments will be conducted to evaluate any effects of the NRL-1 formulation on the nasal mucosa. The following will be assessed on separate scales: nasal irritation, erythema, edema, nasal discharge, mucosal erythema, mucosal edema, nasal discharge, mucosal crusting and epistaxis.

The incidence and severity of TEAEs reported during the study and their relationship to study drug will be tabulated. TEAEs will be coded using the MedDRA and will be presented by body system.

The World Health Organization Drug Dictionary (WHODD) will be used to classify prior and concomitant medications by therapeutic class and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class by dose cohort.

**Assessment of Nasal Irritation:**

Objective evaluations of nasal irritation will be assessed after administration of the intranasal formulation based on the following assessment scale:

| | |
|---|---|
| Grade 0: | No sign of nasal irritation or mucosal erosion |
| Grade 1A: | Focal nasal mucosal irritation or Inflammation |
| Grade 1B: | Superficial mucosal erosion |
| Grade 2: | Moderate mucosal erosion |
| Grade 3: | Ulceration |
| Grade 4: | Septal perforation |

The scoring will be done by a trained observer based on an assessment of the nasal mucosa prior to each dose of NRL-1 and at 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose after each administration, and at discharge. The subjects will also be required to report any incident of nasal irritation or mucosal epistaxis in-between evaluation time points and during follow up contacts.

**Assessment of Mucosal Erythema:**

Objective evaluations of mucosal erythema will be assessed after administration of the intranasal formulation based on the following assessment scale

| | |
|---|---|
| Score 0: | No sign of mucosal erythema |
| Score 1: | Mild mucosal erythema (slight redness) |
| Score 2: | Moderate mucosal erythema (redness) |
| Score 3: | Severe mucosal erythema (marked redness) |

The scoring will be done by a trained observer based on an assessment of the nasal mucosa prior to each dose of NRL-1 and at 30 minutes (± 10 min), and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose after each administration, and at discharge.

**Assessment of Mucosal Edema:**

Objective evaluations of mucosal edema will be assessed after administration of the intranasal formulation based on the following assessment scale

| | |
|---|---|
| Score 0: | No sign of mucosal edema |
| Score 1: | Mild mucosal edema |
| Score 2: | Moderate mucosal edema |
| Score 3: | Severe mucosal edema |

The scoring will be done by a trained observer based on an assessment of the nasal mucosa prior to each dose of NRL-1 and at 30 minutes (± 10 min), and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose after each administration, and at discharge.

**Assessment of Nasal Discharge:**

Objective evaluations of nasal discharge will be assessed after administration of the intranasal formulation based on the following assessment scale

Score 0: No sign of nasal discharge
Score 1: Mild nasal discharge
Score 2: Moderate nasal discharge
Score 3: Severe nasal discharge

The scoring will be done by a trained observer based on an assessment of the nasal mucosa prior to each dose of NRL-1 and at 30 minutes (± 10 min), and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose after each administration, and at discharge.

**Assessment of Mucosal Crusting:**

Objective evaluations of mucosal crusting will be assessed after administration of the intranasal formulation based on the following assessment scale

Score 0: No sign of mucosal crusting
Score 1: Mild mucosal crusting
Score 2: Moderate mucosal crusting
Score 3: Severe mucosal crusting

The scoring will be done by a trained observer based on an assessment of the nasal mucosa prior to each dose of NRL-1 and at 30 minutes (± 10 min), and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose after each administration, and at discharge.

**Assessment of Mucosal Epistaxis:**

Objective evaluations of mucosal epistaxis will be assessed after administration of the intranasal formulation based on the following assessment scale

Score 0: No sign of mucosal epistaxis
Score 1: Mild mucosal epistaxis
Score 2: Moderate mucosal epistaxis
Score 3: Severe mucosal epistaxis

The scoring will be done by a trained observer based on an assessment of the nasal mucosa prior to each dose of NRL-1 and at 30 minutes (± 10 min), and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose after each administration, and at discharge.

**Assessment of Sedation:**

Objective evaluations of sedation will be made using a 6-point ($0 \rightarrow 5$) sedation scoring system that will be used to assess the degree of drowsiness of the subjects after administration of the intranasal formulation. Sedation scores will be reported by the subject (if awake) as well as by a

trained observer, using the same rating scale, prior to each dosing period, at 15 (± 5 min) and 30 minutes (± 10 min), and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose after each administration, and at discharge. Subjects will be also be questioned by the trained observer regarding their degree of drowsiness.

**Assessment of Nasal Mucosal Pain:**

An unconstrained VAS that consists of a 10 cm (100 mm) horizontal straight line will be used to assess acute pain following administration of study drug. The ends of the scale are defined as extreme limits of pain sensation: 0 = no pain, 10 = extreme pain. The subjects will be asked to mark a point on the scale which best describes their intensity of pain and discomfort prior to each dosing period, at 15 (± 5 min) and 30 minutes (± 10 min), and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post-dose, and at discharge. The location of the marking at each time point will be measured and noted as the reported score.

**Columbia Suicide Severity Rating Scale:**

The C-SSRS, a measure of suicidal ideation and behavior, will be used to document suicidality. Suicidality will be assessed at screening (period 1 only), prior to each dosing, and post-dosing at 6 hours. The baseline C-SSRS should be performed within 3 hours prior to dosing of NRL-1. The screening and baseline assessments will use the Baseline/Screening Phase 1 version of the C-SSRS. The Since Last Visit version of the C-SSRS will be used for post-dosing assessments.

**Smell Test:**

A test to evaluate changes in smell will be conducted prior to each dosing, and at 1 hour (± 15 min), 4 hours (± 30 min) post-dose, and at 24 hours (± 30 min) or discharge. The NIH Toolbox for Odor Identification Test will be used as smell tests (1, 2).

## 13.0 DATACOLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

### 13.1 Data Collection and Reporting

A CRF will be completed for each subject who receives at least one dose of study drug. All entries on the CRF must be supported by original source documentation (e.g., laboratory reports, medical records) maintained at the investigational site.

The Investigator will make all safety assessments (AEs, clinical laboratory tests, ECGs, vital signs, and results from physical and neurological examinations) on an ongoing basis. The Investigator is required to review all entries on the CRF and sign at appropriate time intervals.

## 13.2 Study Monitoring

All aspects of the study will be monitored carefully by the Sponsor's designees with respect to cGMP and SOPs for compliance with applicable government regulations. It is the responsibility of the Investigator to provide all study records, including CRFs, source documents, etc., for review and inspection by the clinical monitor.

All CRFs will be verified against corresponding source documentation (e.g., office and clinical laboratory records) for each subject on a risk based approach. Clinical monitors will evaluate periodically the progress of the study, including the verification of appropriate consent form procedures, review of drug accountability and preparation procedures, adherence to dosing procedures, and the verification of the accuracy and completeness of CRFs. Clinical monitors will also ensure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

## 13.3 Data Disclosure and Subject Confidentiality

Subject medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor clinical monitor (or designee), and the IRB/EC.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be identifiable only by coded numbers. Clinical information will not be released without written permission from the subject, except as necessary for monitoring by the IRB/EC, the FDA, or the study Sponsor.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate, to obtain patents in the Sponsor's name covering any of the foregoing.

The results of this study will be published under the direction of the Sponsor. Results will not be published without prior review and approval by the Sponsor.

# 14.0 PROTECTION OF HUMAN SUBJECTS

## 14.1 Basic Principles

This research will be carried out in accordance with the clinical research guidelines established by the Basic Principles defined in the US 21 Code of Federal Regulations (CFR) Parts 11, 50, 56, and 312, the principles enunciated in the Declaration of Helsinki concerning medical research in humans ("Ethical Principles for Medical Research Involving Human Subjects," Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996), and the Good Clinical Practice (GCP) guidelines of the ICH of the Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH E6 (May 1996).

## 14.2 Institutional Review Board/Ethics Committee

The Investigator agrees to provide the IRB/EC with all appropriate material, including a copy of the ICF. The study will not be initiated until the Investigator obtains written approval of the research plan and the ICF from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor. The Sponsor ensures that the IRB/EC complies with the requirements set forth in 21 CFR Part 56.

## 15.0 REFERENCE LIST

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# APPENDIX A: SCHEDULE OF STUDY PROCEDURES

## Appendix A1: Schedule of Study Procedures (Treatment 1): NRL-1 Dose Treatment (During Clinical Site Visit – Seizing Conditions) (Treatment period 1)

| **Study Procedure** | **Screening[a]** | **Baseline[b]** | **Post-Dose Procedures** | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -21 to Day -1** | **Day -7 to Day 0** | **0min** | **15min** | **30min** | **45min** | **1hr** | **1.25hrs** | **1.5hrs** | **1.75hrs** | **2hrs** | **3hrs** | **4hrs** | **5hrs** | **6hrs** | **8hrs*** | **12hrs*** | **Discharge[c]** |
| Signed informed consent | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | | | | | | | | | | | |
| Admission to Clinical Site | | X | | | | | | | | | | | | | | | | |
| Medical history including seizure history | X | X | | | | | | | | | | | | | | | | |
| Columbia-Suicide Severity Rating Scale[d] | X | X | | | | | | | | | | | | | X | | | |
| Physical and Neurological exam (including HEENT) | X | X | | | | | | | | | | | | | | | | |
| Vital signs[e] | X | X | | | | X | | | | | X | | X | | X | X* | X* | X |
| Height and Weight | X | X[f] | | | | | | | | | | | | | | | | |
| EEG (continuous) [g] | | X----------→ | | | | | | | | | | | | | | | | |
| Hematology, Serum Chemistry and Urinalysis | X | X | | | | | | | | | | | | | | | | |
| Serum ß-hCG (Pregnancy)[h] | X | | | | | | | | | | | | | | | | | |
| Urine Pregnancy Test[h] | | X | | | | | | | | | | | | | | | | |
| HIV Antibody and Hepatitis Test[i] | X | | | | | | | | | | | | | | | | | |
| Urine Drug and Alcohol Screen[j] | X | X | | | | | | | | | | | | | | | | |
| Prior and Concomitant medication assessment | X | X | X----------→ | | | | | | | | | | | | | | | |
| Adverse event assessment[k] | | | X----------→ | | | | | | | | | | | | | | | |
| ECG (12-Lead in triplicate)[l] | X | X | | | | | | | | | | | | | | | | |
| **NRL-1 administration** | | | **X** | | | | | | | | | | | | | | | |
| Blood Sample for PK[m,n] | | X | X[l] | X | X | X | X | X | X | X | X | X | X | X | X | X* | X* | |
| Nasal Irritation[o] | | X | | | | | | | | | X | | X | | X | | | X |
| Nasal Examinations[p] | | X | | | X | | X | | | | X | | X | | X | | | X |
| Sedation Score[q] | | X | | X | X | | X | | | | X | | X | | X | | | X |
| Smell Test [r] | | X | | | | | X | | | | | | X | | | | | X |
| VAS for Pain[s] | | X | | X | X | | X | | | | X | | X | | X | | | X |

* Optional assessment if feasible.

a. Screening evaluations must be performed within 21 days prior to dosing on Day 0. Screening evaluations performed within 7 days (Day -7 to Day 0) of dosing do not need to be repeated if subjects are maintained in house. Screening procedures are performed only once prior to the first dose of study medication (Treatment 1 or 2).
b. Baseline evaluations will be performed upon admission to the clinical site and within 7 days of dosing if maintained in house. Time point 0 will be considered the time of dosing NRL-1 and initiation of PK blood sampling. Subjects may be dosed in either Treatment 1 or Treatment 2 first. The second treatment with NRL-1 will be separated by a minimum 14-day wash out period and baseline evaluation will be repeated for each treatment period (if subjects are on oral contraceptives (OC) the period between dosing should be extended to approximately 28-days to ensure that the subject is dosed at the same approximate time of the OC cycle).
c. Discharge occurs anytime after the PK blood sample is taken at 6 hours post dose (or optional 8 and 12 hours). When discharge occurs after 6 hours post dose, the assessments at discharge that overlap with the assessments at 6 hours post dose do not have to be repeated. In that case, check the check box in the CRF at 6 hours post dose to confirm that the assessments that overlap with the assessments at discharge is not going to be repeated.
d. Suicidal events will be assessed using the C-SSRS (adult or children) at screening, baseline, and at 6 hours post dose. The baseline C-SSRS should be performed within 3 hours prior to dosing of NRL-1 (see APPENDIX C).
e. Vital signs (temperature, pulse, respiratory rate and blood pressure) are to be obtained at screening, baseline, and at 45 (± 5 min) minutes, 2 (± 15 min), 4 (± 30 min), 6 (± 30 min), 8 (± 30 min), and 12 (± 30 min) hours post dosing, and at discharge. Vital signs at 8 and 12 hours are optional.
f. Weight only.
g. Subjects will be monitored for seizure activity with a continuous EEG evaluation. The EEG is considered standard of care when in the EMU setting, but is part of the study procedures if in a CTRC setting. The start time, stop time, and type of seizure will be recorded based on the EEG results. The time of NRL-1 dosing will also be recorded as part of the study database.
h. A serum (ß-hCG) pregnancy test will be administered to females of childbearing potential at screening. Urine pregnancy test is only required for female subjects of child bearing potential. If a serum pregnancy test is done on Day -1, urine pregnancy test does not have to be repeated on Day 0 (baseline). Pregnancy testing does not have to be done on subjects age 6 to 11.
i. Hepatitis B surface antigen (HbSAg), or Hepatitis C
j. When marijuana was used for medical reasons in the opinion of the investigator, it is not considered as drug abuse and the patient can be enrolled even if the marijuana metabolites in the urine revealed as positive. In this case, information about marijuana use should be entered in the CRF page for concomitant medication.
k. Adverse event assessment is continuous from time of first dose of NRL-1.
l. ECG is to be performed in triplicate. Three consecutive ECGs (each approximately 1-2 minutes apart) are performed.
m. Blood samples (3 mL each) are to be obtained before dosing (0, pre-dose) and at 15, 30, and 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, and 6 hours. Blood samples should also be obtained if feasible at 8 and 12 hours after dosing. If a blood sample collection is delayed, then the collection will occur as soon as feasible and should not be 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 samples.
n. If a second dose of NRL-1 is administered due to a subsequent seizure btween 4 and 12 hours after the initial dose, when clinically feasible, PK samples should be collected based on the time of the second dose at 0, 30 minutes, and 1, 2, and 4 hours after dosing.
o. Nasal Irritation assessments are performed prior to dosing (baseline) and at 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge.
p. Nasal examination and scoring for mucosal erythema, mucosal edema, nasal discharge, mucosal crusting and mucosal epistaxis will be performed prior to dosing (baseline) and at 30 (± 10 min) minutes, 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge.
q. Sedation Scores are just prior to dosing (baseline) and at 15 (± 5 min) and 30 (± 10 min) minutes, 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge.
r. Smell tests and examination of the nasal mucosa will be conducted at baseline, and at 1 hour (± 15 min), 4 hours (± 30 min) post dose, and at discharge. The NIH Toolbox Odor Identification Test will be used as smell tests (1, 2).
s. VAS Scores are just prior to dosing (baseline) and at 15 (± 5 min) and 30 (± 10 min) minutes, 1(± 10 min), 2 (± 15 min), 4 (± 30 min), 6 (± 30 min) hours post dose, and at discharge.

## Appendix A2: Schedule of Study Procedures (Treatment 2): NRL-1 Dose Treatment (Non-Seizing [Normative] Conditions)

| **Study Procedure** | **Baseline[a]** | **Post-Dose Procedures** | | | | | | | | | | | | | | | | **Follow-up Telephone Contact[m]** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day 14** | **0 min** | **15min** | **30min** | **45min** | **1hr** | **1.25hrs** | **1.5hrs** | **1.75hrs** | **2hrs** | **3hrs** | **4hrs** | **5hrs** | **6hrs** | **8hrs*** | **12hrs*** | **Discharge[l]** | **Day 21** | **Day 28** |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | | | | | | | |
| Admission to Clinical Unit | X | | | | | | | | | | | | | | | | | | |
| Columbia-Suicide Severity Rating Scale[k] | X | | | | | | | | | | | | | X | | | | | |
| Physical and Neurological exam (including HEENT) | X | | | | | | | | | | | | | | | | | | |
| Vital signs[b] | X | | | | X | | | | | X | | X | | X | X* | X* | X | | |
| Weight | X | | | | | | | | | | | | | | | | | | |
| Hematology, Serum Chemistry and Urinalysis | X | | | | | | | | | | | | | | | | | | |
| Urine Pregnancy Test[c] | X | | | | | | | | | | | | | | | | | | |
| Urine Drug, Alcohol and Cotinine Screen[o] | X | | | | | | | | | | | | | | | | | | |
| Prior and Concomitant medication assessment | X | X----------→ | | | | | | | | | | | | | | | | | |
| Adverse event assessment[d] | X | X----------→ | | | | | | | | | | | | | | | | | |
| ECG (12-Lead in triplicate)[e] | X | | | | | | | | | | | | | | | | | | |
| **NRL-1 administration** | | **X** | | | | | | | | | | | | | | | | | |
| Blood Sample for PK[f] | X | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X* | X* | | | |
| Nasal Irritation[g] | X | | | | | | | | | X | | X | | X | | | X | | |
| Nasal Examinations[h] | X | | | X | | X | | | | X | | X | | X | | | X | | |
| Sedation Score Assessment[i] | X | | X | X | | X | | | | X | | X | | X | | | X | | |
| Smell Test [n] | X | | | | | X | | | | | | X | | | | | X | | |
| VAS for Pain[j] | X | | X[k] | X | | X | | | | X | | X | | X | | | X | | |

* Optional assessment if feasible.

a. Baseline evaluations will be performed within 48 hours prior to dosing NRL-1. The Day 14 visit may be between 14 and 28 days after the initial dosing of NRL-1.
b. Follow-up phone calls 7 days (± 2 days) and 14 days (± 3 days) after the second dose of NRL-1 dosing to determine if any AE has occurred and to follow-up on any TEAEs ongoing since last communication with the subject. Subjects who prematurely discontinued will be followed up by phone calls approximately 7 days (± 2 days) after the last dose of NRL-1.
c. Discharge occurs anytime after the PK blood sample is taken at 6 hours post dose (or optional 8 and 12 hours). When discharge occurs after 6 hours post dose, the assessments at discharge that overlap with the assessments at 6 hours post dose do not have to be repeated. In that case, check the check box in the CRF at 6 hours post dose to confirm that the assessments that overlap with the assessments at discharge is not going to be repeated.
d. Suicidal events will be assessed using the C-SSRS (adult or children) at screening and baseline, and at 6 hours post dose. The baseline C-SSRS should be performed within 3 hours of administering the dose (see APPENDIX C).
e. Vital signs (temperature, pulse, respiratory rate and blood pressure) are to be obtained at baseline and at 45 (± 5 min), 2 (± 15 min), 4 (± 30 min), 6 (± 30 min), 8 (± 30 min), and 12 (± 30 min) hours post dosing and at discharge. Vital signs at 8, 12 hours are optional.
f. Pregnancy test is only required for female subjects of child bearing potential. Pregnancy test does not have to be done on subjects age 6 to 11.
g. When marijuana is used for medical reason in the opinion of the investigator, it is not considered as drug abuse and the patient can be enrolled even if the marijuana metabolites in the urine revealed as positive. In this case, information about marijuana use should be entered in the CRF page for concomitant medication.
h. Adverse event assessment is continuous.
i. ECG is to be performed in triplicate. Three consecutive ECGs (each approximately 1-2 minutes apart) are performed as part of the screening process.
j. Blood samples are to be obtained before dosing (0, pre-dose) and at 15, 30, and 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, and 6 hours. Blood samples should also be obtained if feasible at 8, 12 hours. 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 8 hour samples, 3) and ± 30 minutes for the 8 and12 hour sample.
k. Nasal Irritation assessments are performed prior to dosing (baseline) and at 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge.
l. Nasal examination and scoring for mucosal erythema, mucosal edema, nasal discharge, mucosal crusting and mucosal epistaxis will be performed prior to dosing (baseline) and at 30 (± 10 min) minutes, 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge.
m. Sedation Scores are just prior to dosing (baseline) and at 15 (± 5 min) and 30 (± 10 min) minutes, and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge.
n. Smell tests and examination of the nasal mucosa will be conducted at baseline, and at 1 hour (± 10 min), 4 hours (± 30 min), and at discharge. The NIH Toolbox Odor Identification Test will be used as smell tests (1, 2).
o. VAS Scores are just prior to dosing (baseline) and at 15 (± 5 min) and 30 (± 10 min) minutes, and 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge.

# APPENDIX B: SEDATION SCORING

## Appendix B: Sedation Scoring

A sedation scale will be used to assess the degree of drowsiness of the subjects after administration of the intranasal and intravenous diazepam formulations.

Sedation scores will be reported by the subject (if awake) as well as by a trained observer using the same rating scale, just at (baseline) and at 15 and 30 minutes, and 1, 2, 4, and 6 hours post dose and at discharge.

**Sedation Scale**

0 - Alert, not drowsy; normal conversation

1 - Awake, talking; but somewhat drowsy

2 - Napping or sleeping, but easily awakened

3 - Sleeping, awakened only with loud voice or shaking

4 - Sleeping, very difficult to awaken; promptly returns to sleep

5 - Sleeping, cannot awaken

# APPENDIX C: COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

## Appendix C: Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS), a measure of suicidal ideation and behavior, will be used to document suicidality. For adults, screening and baseline assessments will use the **Baseline/Screening Phase 1** version of the C-SSRS. The Since Last Visit version of the C-SSRS will be used for post-dosing assessments. For children, screening and baseline assessments will use Children's Baseline/Screening and Children's Since Last Visit will be used for post-dosing assessments.

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

## Baseline/Screening Version

Version 1/14/09

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.***

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in* ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu*

| ***SUICIDAL IDEATION*** | | |
|---|---|---|
| *Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.* | **Lifetime: Time He/She Felt Most Suicidal** | **Past 6 Months** |
| **1. Wish to be Dead**<br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br>***Have you wished you were dead or wished you could go to sleep and not wake up?***<br><br>If yes, describe: | **Yes No**<br>☐ ☐ | **Yes No**<br>☐ ☐ |
| **2. Non-Specific Active Suicidal Thoughts**<br>General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br>***Have you actually had any thoughts of killing yourself?***<br><br>If yes, describe: | **Yes No**<br>☐ ☐ | **Yes No**<br>☐ ☐ |
| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**<br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*<br>***Have you been thinking about how you might do this?***<br><br>If yes, describe: | **Yes No**<br>☐ ☐ | **Yes No**<br>☐ ☐ |
| **4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**<br>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*<br>***Have you had these thoughts and had some intention of acting on them?***<br><br>If yes, describe: | **Yes No**<br>☐ ☐ | **Yes No**<br>☐ ☐ |
| **5. Active Suicidal Ideation with Specific Plan and Intent**<br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br>***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***<br><br>If yes, describe: | **Yes No**<br>☐ ☐ | **Yes No**<br>☐ ☐ |
| ***INTENSITY OF IDEATION*** | | |
| *The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.*<br><br>Lifetime - ***Most Severe Ideation:*** _____<br>_____<br>***Type # (1-5)*** ***Description of Ideation***<br><br>Past 6 Months - ***Most Severe Ideation:*** _____<br>_____<br>***Type # (1-5)*** ***Description of Ideation*** | Most Severe | Most Severe |
| **Frequency**<br>***How many times have you had these thoughts?***<br>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day | ____ | ____ |
| **Duration**<br>***When you have the thoughts how long do they last?***<br>(1) Fleeting - few seconds or minutes<br>(2) Less than 1 hour/some of the time<br>(3) 1-4 hours/a lot of time<br>(4) 4-8 hours/most of day<br>(5) More than 8 hours/persistent or continuous | ____ | ____ |
| **Controllability**<br>***Could/can you stop thinking about killing yourself or wanting to die if you want to?***<br>(1) Easily able to control thoughts<br>(2) Can control thoughts with little difficulty<br>(3) Can control thoughts with some difficulty<br>(4) Can control thoughts with a lot of difficulty<br>(5) Unable to control thoughts<br>(0) Does not attempt to control thoughts | ____ | ____ |

| | | |
|---|---|---|
| **Deterrents**<br>***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?***<br>(1) Deterrents definitely stopped you from attempting suicide<br>(2) Deterrents probably stopped you<br>(3) Uncertain that deterrents stopped you<br>(4) Deterrents most likely did not stop you<br>(5) Deterrents definitely did not stop you<br>(0) Does not apply | ____ | ____ |
| ***INTENSITY OF IDEATION*** | | |
| **Reasons for Ideation**<br>***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?***<br>(1) Completely to get attention, revenge or a reaction from others<br>(2) Mostly to get attention, revenge or a reaction from others<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain<br>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(0) Does not apply | ____ | ____ |

Version 1/14/09

| ***SUICIDAL BEHAVIOR***<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | **Lifetime** |
|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>***Have you made a suicide attempt?***<br>***Have you done anything to harm yourself?***<br>***Have you done anything dangerous where you could have died?***<br>***What did you do?***<br>***Did you_____ as a way to end your life?***<br>***Did you want to die (even a little) when you_____?***<br>***Were you trying to end your life when you _____?***<br>***Or Did you think it was possible you could have died from_____?***<br>***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better,***<br>***get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent)<br>If yes, describe:<br><br>**Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | **Yes No**<br>☐ ☐<br><br>Total # of Attempts<br>_____<br><br>**Yes No**<br>☐ ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***<br>If yes, describe: | **Yes No**<br>☐ ☐<br><br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?***<br>If yes, describe: | **Yes No**<br>☐ ☐<br><br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?***<br>If yes, describe: | **Yes No**<br>☐ ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | **Yes No**<br>☐ ☐ |

| ***Answer for Actual Attempts Only*** | Most Recent Attempt Date: | Most Lethal Attempt Date: | Initial/First Attempt Date: |
|---|---|---|---|
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality=0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

**Since Last Visit**

Version 1/14/09

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.***

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in* ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu*

| ***SUICIDAL IDEATION*** | |
|---|---|
| *Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.* | Post-Dose |
| **1. Wish to be Dead**<br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br>***Have you wished you were dead or wished you could go to sleep and not wake up?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ |
| **2. Non-Specific Active Suicidal Thoughts**<br>General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br>***Have you actually had any thoughts of killing yourself?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ |
| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**<br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*<br>***Have you been thinking about how you might do this?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ |
| **4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**<br>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*<br>***Have you had these thoughts and had some intention of acting on them?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ |
| **5. Active Suicidal Ideation with Specific Plan and Intent**<br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br>***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ |
| ***INTENSITY OF IDEATION*** | |
| *The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).*<br><br>***Most Severe Ideation:*** _____<br>_____<br>***Type # (1-5)*** ***Description of Ideation*** | Most Severe |
| **Frequency**<br>***How many times have you had these thoughts?***<br>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day | ____ |
| **Duration**<br>***When you have the thoughts, how long do they last?***<br>(1) Fleeting - few seconds or minutes<br>(2) Less than 1 hour/some of the time<br>(3) 1-4 hours/a lot of time<br>(4) 4-8 hours/most of day<br>(5) More than 8 hours/persistent or continuous | ____ |
| **Controllability**<br>***Could/can you stop thinking about killing yourself or wanting to die if you want to?***<br>(1) Easily able to control thoughts<br>(2) Can control thoughts with little difficulty<br>(3) Can control thoughts with some difficulty<br>(4) Can control thoughts with a lot of difficulty<br>(5) Unable to control thoughts<br>(0) Does not attempt to control thoughts | ____ |

| | |
|---|---|
| **Deterrents**<br>***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?***<br>(1) Deterrents definitely stopped you from attempting suicide<br>(2) Deterrents probably stopped you<br>(3) Uncertain that deterrents stopped you<br>(4) Deterrents most likely did not stop you<br>(5) Deterrents definitely did not stop you<br>(0) Does not apply | ____ |
| ***INTENSITY OF IDEATION*** | |
| **Reasons for Ideation**<br>***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?***<br>(1) Completely to get attention, revenge or a reaction from others<br>(2) Mostly to get attention, revenge or a reaction from others<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain<br>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(0) Does not apply | ____ |

Version 1/14/09

| ***SUICIDAL BEHAVIOR***<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | Post-Dose |
|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>***Have you made a suicide attempt?***<br>***Have you done anything to harm yourself?***<br>***Have you done anything dangerous where you could have died?***<br>***What did you do?***<br>***Did you_____ as a way to end your life?***<br>***Did you want to die (even a little) when you_____?***<br>***Were you trying to end your life when you _____?***<br>***Or did you think it was possible you could have died from_____?***<br>***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent)<br>If yes, describe:<br><br>**Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | **Yes** **No**<br>☐ ☐<br><br>Total # of Attempts<br>_____<br><br>**Yes** **No**<br>☐ ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***<br>If yes, describe: | **Yes** **No**<br>☐ ☐<br><br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?***<br>If yes, describe: | **Yes** **No**<br>☐ ☐<br><br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?***<br>If yes, describe: | **Yes** **No**<br>☐ ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | **Yes** **No**<br>☐ ☐ |
| **Suicide:** | **Yes** **No**<br>☐ ☐ |

| ***Answer for Actual Attempts Only*** | Most Lethal Attempt Date: |
|---|---|
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality=0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ |

References

K Posner; MA Oquendo; M Gould; B Stanley; M Davies. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants, Am J Psychiatry, 2007; 164:1035-1043.

Center for Drug Evaluation and Research (CDER), Guidance for Industry Suicidality: Prospective Assessment of Occurrence in Clinical Trials. September 2010.

K Posner; GK Brown; B Stanley; DA Brent; KV Yershova; MA Oquendo; GW Currier; GA Melvin; L Greenhill; S Shen; JJ Mann. The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. Am J Psychiatry 2011;168:1266-1277.

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

## Children's Baseline/Screening

Version 6/23/10

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.***

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in* ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact *posnerk@nyspi.columbia.edu*

| ***SUICIDAL IDEATION*** | | |
|---|---|---|
| *Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.* | **Lifetime** | **Past 6 Months** |
| **1. Wish to be Dead**<br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br>***Have you thought about being dead or what it would be like to be dead?***<br>***Have you wished you were dead or wished you could go to sleep and never wake up?***<br>***Do you ever wish you weren't alive anymore?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ | **Yes** ☐ **No** ☐ |
| **2. Non-Specific Active Suicidal Thoughts**<br>General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br>***Have you thought about doing something to make yourself not alive anymore?***<br>***Have you had any thoughts about killing yourself?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ | **Yes** ☐ **No** ☐ |
| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**<br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*<br>***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ | **Yes** ☐ **No** ☐ |
| **4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**<br>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*<br>***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?***<br>***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ | **Yes** ☐ **No** ☐ |
| **5. Active Suicidal Ideation with Specific Plan and Intent**<br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br>***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?***<br>***What was your plan?***<br>***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ | **Yes** ☐ **No** ☐ |
| ***INTENSITY OF IDEATION*** | | |
| *The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).*<br><br>***Most Severe Ideation:*** _____ _____<br>***Type # (1-5)*** ***Description of Ideation*** | Most Severe | Most Severe |
| **Frequency**<br>***How many times have you had these thoughts?*** ***Write response*** _____<br>(1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable | ____ | ____ |

| ***SUICIDAL BEHAVIOR***<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | **Lifetime** |
|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>***Did you ever do anything to try to kill yourself or make yourself not alive anymore? What did you do?***<br>***Did you ever hurt yourself on purpose? Why did you do that?***<br>***Did you_____ as a way to end your life?***<br>***Did you want to die (even a little) when you_____?***<br>***Were you trying to make yourself not alive anymore when you _____?***<br>***Or did you think it was possible you could have died from_____?***<br>***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent)<br>If yes, describe:<br><br>**Has subject engaged in Non-Suicidal Self-Injurious Behavior?**<br><br>**Has subject engaged in Self-Injurious Behavior, intent unknown?** | **Yes No**<br>☐ ☐<br><br>Total # of Attempts<br>_____<br><br>**Yes No**<br>☐ ☐<br>**Yes No**<br>☐ ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?***<br>If yes, describe: | **Yes No**<br>☐ ☐<br><br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?***<br>If yes, describe: | **Yes No**<br>☐ ☐<br><br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?***<br>If yes, describe: | **Yes No**<br>☐ ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | **Yes No**<br>☐ ☐ |

| *Answer for Actual Attempts Only* | Most Recent Attempt Date: | Most Lethal Attempt Date: | Initial/First Attempt Date: |
|---|---|---|---|
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality=0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br><br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.***

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in* ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

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| *SUICIDAL IDEATION* | |
|---|---|
| *Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.* | **Since Last Visit** |
| **1. Wish to be Dead**<br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br>***Have you thought about being dead or what it would be like to be dead?***<br>***Have you wished you were dead or wished you could go to sleep and never wake up?***<br>***Do you wish you weren't alive anymore?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ |
| **2. Non-Specific Active Suicidal Thoughts**<br>General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br>***Have you thought about doing something to make yourself not alive anymore?***<br>***Have you had any thoughts about killing yourself?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ |
| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**<br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*<br>***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ |
| **4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**<br>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*<br>***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?***<br>***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ |
| **5. Active Suicidal Ideation with Specific Plan and Intent**<br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br>***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?***<br>***What was your plan?***<br>***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?***<br><br>If yes, describe: | **Yes** ☐ **No** ☐ |
| *INTENSITY OF IDEATION* | |
| *The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).*<br><br>***Most Severe Ideation:*** _____ _____<br>***Type # (1-5)*** ***Description of Ideation*** | Most Severe |
| **Frequency**<br>***How many times have you had these thoughts?*** ***Write response*** _____<br>(1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable | ____ |

| *SUICIDAL BEHAVIOR*<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | **Since Last Visit** |
|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?***<br>***Did you hurt yourself on purpose? Why did you do that?***<br>***Did you_____ as a way to end your life?***<br>***Did you want to die (even a little) when you_____?***<br>***Were you trying to make yourself not alive anymore when you _____?***<br>***Or did you think it was possible you could have died from_____?***<br>***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent)<br>If yes, describe:<br><br>**Has subject engaged in Non-Suicidal Self-Injurious Behavior?**<br><br>**Has subject engaged in Self-Injurious Behavior, intent unknown?** | **Yes No**<br>☐ ☐<br><br>Total # of Attempts<br>____<br><br>**Yes No**<br>☐ ☐<br>**Yes No**<br>☐ ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.<br>Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?***<br>If yes, describe: | **Yes No**<br>☐ ☐<br><br>Total # of interrupted<br>____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?***<br>If yes, describe: | **Yes No**<br>☐ ☐<br><br>Total # of aborted<br>____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?***<br>If yes, describe: | **Yes No**<br>☐ ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | **Yes No**<br>☐ ☐ |
| **Completed Suicide:** | **Yes No**<br>☐ ☐ |

# APPENDIX D: NIH TOOLBOX ODOR IDENTIFICATION TEST

This test assesses a person's ability to identify various odors. Participants use scratch 'n' sniff cards and after scratching them one at a time, are asked to identify which of four pictures on the computer screen matches the odor they have just smelled.

Participants ages 10-85 are administered nine odor cards, while those ages 3-9 are administered five odor cards. Child participants (ages 3 -9 years) are first asked to identify the eight pictures that are used as answer choices, to ensure they can complete the task. Having identified the pictures, they are asked if they have tasted or smelled the objects or foods depicted.

This test takes approximately 4 to 5 minutes to administer and is recommended for ages 3-85.

**http://www.nihtoolbox.org/WhatAndWhy/Sensation/Olfaction/Pages/NIH-Toolbox-Odor-Identification-Test.aspx**

# APPENDIX E: LIST OF PROHIBITED MEDICATION

| | |
|---|---|
| Amiodarone | Ketoconazole |
| Amprenavir | Lopinavir/Ritonavir |
| Aprepitant | Methoxsalen |
| Atazanavir | Mexiletine |
| Boceprevir | Mibefradil |
| Bupropion | Miconazole |
| Cinacalcet | Moclobemide |
| Ciprofloxacin | Nefazodone |
| Clarithromycin | Nelfinavir |
| Conivaptan | Omeprazole |
| Darunavir/Ritonavir | Oxandrolone |
| Diltiazem | Paroxetine |
| Duloxetine | Phenylpropanolamine |
| Enoxacin | Posaconazole |
| Erythromycin | Quinidine |
| Esomeprazole | Ritonavir |
| Fluconazole | Saquinavir |
| Fluoxetine | Telaprevir |
| Fluvoxamine | Telithromycin |
| Fosamprenavir | Terbinafine |
| Gemfibrozil | Thiabendazole |
| Grapefruit Juice | Ticlopidine |
| Imatinib | Verapamil |
| Indinavir | Voriconazole |
| Itraconazole | Zileuton |