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| STUDY TITLE: | A 12-Month Open-Label, Repeat-Dose Safety Study of NRL-1 in Epilepsy Subjects |
| STUDY PHASE: | Phase 3 |
| PROTOCOL NUMBER: | DIAZ.001.05 |
| | NCT Number: NCT02721069 |
| | Protocol Version 4.0 - 28 September 2017 |

# NEURELIS, INC.

# INVESTIGATIONAL NEW DRUG PROTOCOL

# NRL-1 (INTRANASAL DIAZEPAM)

**PROTOCOL NUMBER DIAZ.001.05**
**VERSION 4**
**28 SEPTEMBER 2017**

**A 12-MONTH, OPEN-LABEL, REPEAT-DOSE SAFETY STUDY OF NRL-1 IN EPILEPSY SUBJECTS**

**SPONSOR:**

**NEURELIS INC.**
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# CONFIDENTIAL

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| ABBREVIATION | DEFINITION |
|---|---|
| AE | adverse event |
| AEDs | antiepileptic drugs |
| ARS | acute repetitive seizures |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| $AUC_{0-t}$ | area under the plasma concentration-time curve from 0 to t hours |
| $AUC\infty$ | area under the plasma concentration-time curve to infinity |
| ß-hCG | serum pregnancy test |
| BUN | blood urea nitrogen |
| 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 |
| $C_{max}$ | Maximum plasma concentration |
| CNS | central nervous system |
| $CO_2$ | bicarbonate/carbon dioxide |
| CRF | case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DFU | Directions for Use |
| E.coli | Escherichia coli |
| ECG | Electrocardiogram |
| EPA | Environmental Protection Agency |
| FDA | US Food and Drug Administration |
| GABA | gamma-aminobutyric acid |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |

| ABBREVIATION | DEFINITION |
|---|---|
| GRAS | generally recognized as safe |
| HbSAg | Hepatitis B surface antigen |
| HEENT | head, ears, eyes, nose, and throat |
| 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) |
| $LD_{50}$ | lethal dose 50% or median lethal dose |
| LDH | lactate dehydrogenase |
| MRHD | maximum recommended human dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram(s) |
| mL | milliliter |
| NOEL | no observable effect level |
| NRL-1.A | 100 mg/mL diazepam nasal spray suspension manufactured for Neurelis, Inc. |
| NRL-1.B | 100 mg/mL diazepam nasal spray solution manufactured for Neurelis, Inc. |
| OECD | Organisation for Economic Co-operation and Development |
| PBMC | blood peripheral mononuclear cells |
| PI | principal investigator |
| PK | pharmacokinetics |
| QOLIE | Quality of Life in Epilepsy |
| RBC | red blood cell |
| SAE | serious adverse event |
| SD | Standard Deviation |

| ABBREVIATION | DEFINITION |
|---|---|
| SOP | standard operating procedure |
| TEAE | treatment-emergent adverse event |
| $t_{1/2}$ | mean elimination half-life |
| $t_{max}$ | time to maximum plasma concentration |
| µL | microliter |
| UDS | unit dose sprayer |
| US/USA | United States of America |
| 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** | A 12-Month Open-Label, Repeat-Dose Safety Study of NRL-1 in Epilepsy Subjects (DIAZ.001.05) |
| **Phase** | Phase 3 |
| **Study Drug** | NRL-1 (Intranasal Diazepam) |
| **Objectives** | Primary objective:<br>• The primary objective of this study is to assess the safety of diazepam after repeat intranasal doses of NRL-1 administered to Epilepsy subjects who experience frequent breakthrough seizures or Acute Repetitive Seizures (ARS), over a 12-month period.<br>Secondary objective:<br>• To assess the tolerability of diazepam after repeat intranasal administration of NRL-1;<br>• To assess the ability of caregivers to administer NRL-1 based on the Directions for Use (DFU) (see APPENDIX E.);<br>To assess an improvement in the Quality of Life with NRL-1 use as compared to Diastat. |
| **Study Design** | This is a Phase 3, repeat dose, open-label, safety study in Epilepsy subjects who have frequent breakthrough seizures or ARS. NRL-1 will be administered as needed to treat bouts of those seizures over a 12-month period of time. Doses will be defined as 5 milligrams (mg), 10 mg, 15 mg, or 20 mg based on the subject's body weight. The dosage may be increased or decreased for efficacy or safety reasons, if determined by the Principal Investigator that a different dose is necessary and there is no safety concern. A diary will be used to record the seizure and NRL-1 administration.<br>The study consists of a screening phase, a baseline, a 12-month treatment period and a follow-up telephone contact 28-days after the last dose of NRL-1 or at study termination. The primary purpose of this study is to assess the safety of repeat doses of NRL-1 as intermittent chronic therapy to treat frequent break through seizures or ARS. Subjects will return to the site per the Schedule of Events with all study visits having a ±7 day window around visits.<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 ECGs, and AE assessment. Concomitant medications will be recorded. Columbia-Suicide Severity Rating Scale (C-SSRS for adults or pediatric), Nasal Examination and Irritation Assessment (The following will be assessed on separate scales: nasal irritation, nasal discharge, mucosal erythema, mucosal edema, mucosal crusting and mucosal epistaxis), Sedation Score Assessment, and Smell Test (NIH Toolbox Odor Identification Test, (1, 2) will be conducted at each visit. A targeted physical examination may be used to evaluate any potentially related side effects.<br>Subjects and caregivers will be trained on the proper use of the NRL-1 nasal sprayer at screening period and as needed during treatment period. The ability of caregivers to administer NRL-1 based on the Directions for Use (DFU) will be assessed (see APPENDIX E).<br>The Quality of Life in Epilepsy (QOLIE) questionnaire will be administered to assess the quality of life while on NRL-1 compared to baseline therapy at time of enrollment.<br>Naïve subjects may be entered into this study as well as those subjects completing the protocol DIAZ.001.04 are eligible for the long-term safety study (DIAZ.01.05) and may receive treatment with NRL-1 under DIAZ.01.05 protocol. |
| **Sample Size** | Up to 100 subjects, at least 30 age 6 to 11 years and up to 70 over 12 years of age, are to be enrolled. |
| **Study Population** | Subjects with a clinical diagnosis of frequent break through seizures or ARS with bouts of uncontrolled seizures, 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. Subject has a clinical diagnosis of Epilepsy and while on a stable regimen of anti-epileptic medication, still experiences bouts of seizures (e.g. frequent break through seizures or ARS), and who, in the opinion of the Investigator, may need benzodiazepine intervention for seizure control 1 time every other month on average (i.e. average 6 times a year).<br>4. Subject has a qualified caregiver or medical professional available that can administer study medication in the event of a seizure.<br>5. Subjects having either partial or generalized Epilepsy with motor seizures or seizures with clear alteration of awareness.<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). Subjects must have used the same method for at least one (1) month prior to starting the study.<br>7. No clinically significant abnormal findings in the medical history, on the physical examination or electrocardiogram (QTcF<450 msec for males and QTcF<470 msec for females).<br>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. |
| **Main Exclusion Criteria** | Subjects must **NOT** meet any of the following Exclusion criteria to be eligible for enrollment:<br>1. A history of clinically significant gastrointestinal, renal, hepatic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject.<br>2. Subject has had significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening.<br>3. Subjects with active major depression or a past suicide attempt, or any Suicidal Ideation of 3, 4, or 5 or any Suicidal Behavior in Lifetime using Columbia-Suicide Severity Rating Scale (C-SSRS). The pediatric 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>4. A history of allergic or adverse responses to diazepam or any comparable or similar product.<br>5. Participation in a clinical trial other than protocol DIAZ.001.04 within 30 days prior to Day 0. Participation in an observational (non-interventional) study is not excluded as long as there are no scheduling conflicts with this study.<br>6. Positive serum pregnancy test (ß-hCG) at screening for subjects age 12 or greater.<br>Positive blood screen for Human immunodeficiency virus (HIV), Hepatitis B surface antigen (HbSAg), or Hepatitis C, or a positive urine screen for alcohol, or drugs of abuse, except marijuana use for medical reasons. 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. |

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| **Dosage and Administration of Study Drug** | The initial 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/milliliter [mL], 100 microliters [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).<br>A second dose may be administered if needed 4-12 hours after the initial dose of NRL-1. Additionally, the dosage may be increased or decreased for efficacy or safety reasons, if determined by the Principal Investigator that a different dose is necessary and there is no safety concern. |
| **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, nasal irritation and examination, and C-SSRS.<br>AE collection will begin on Day 0 after baseline assessments are complete prior to the initial treatment with NRL-1 and continue for 28-days after study termination. 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. AEs that occur after dosing in a home setting will be recorded in a diary and reported at the next study visit. Subjects will receive follow-up telephone contact approximately 28 days (± 3 days) after study termination to determine if any AE has occurred and to follow-up on any TEAEs ongoing since last communication with the subject.<br>Nasal irritation will be assessed at baseline and each study visit as well as based on reports of any nasal mucosal AEs between visits to the clinical site. Smell tests will be conducted at baseline and at each study visit. The NIH Toolbox Odor Identification Test will be used as smell test in this study (1, 2).<br>The C-SSRS for adults and pediatrics, a measure of suicidal ideation and behavior, will be used to document suicidality in order to classify suicidal events. Suicidality will be assessed at screening for eligibility (see APPENDIX B).<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. |

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| | 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. |
| **Study Duration** | It is planned that each subject will participate in the primary safety portion of the study for up to 414-days, which comprises a 21-day screening period, baseline, a treatment period of up to 365-days, and follow-up period up to 28 days. Subjects may be continued on treatment beyond Day 365 at the discretion of the investigator and approval of the sponsor. For treatment beyond Day 365, it is recommended that subjects are contacted by the Investigator at least each 3 months to obtain information on any adverse events. Study visits after Day 365 for safety assessment will be recorded in the EDC (CRF) as Unscheduled visits. |
| **Study Centers** | Up to twenty (20) centers will enroll patients. |

# 1.0 INTRODUCTION

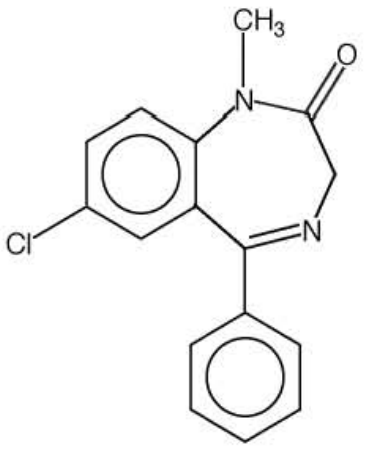
Epilepsy is a significant health problem affecting 50 million people worldwide, including 2.7 million Americans. Epilepsy negatively impacts quality of life and increases morbidity and mortality. In the US, 25-50,000 deaths each year are attributed to seizures and related causes.

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 pharmacokinetic 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 pharmacokinetic 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 these studies.

### 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-aminobutyric acid (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 milligrams (mg)/kilogram (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 microliters [µL] dose volume of 100 mg diazepam per milliliter [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/m 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 the 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 – 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 oberservable 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 IV 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 IV 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 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.

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.

**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) |
| $\lambda z$ ($h^{-1}$) | 20 | 0.0142 (0.0053) | 20 | 0.0155 (0.0046) | 24 | 0.0142 (0.0055) |
| $t_{½}$ (h) | 20 | 56.2 (23.0) | 20 | 49.2 (16.9) | 24 | 56.2 (21.0) |

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

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 treatment-related AEs 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 adverse event. 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 3 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 (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 and 7 mg in polyethylene glycol 300 in seven healthy volunteers as compared to a 5 mg IV dose. The intranasal formulation had a relative bioavailability of 45% and 42%, a $C_{max}$ of 99 and 179 ng⁄mL and a $t_{max}$ of 18 and 42 minutes for the 4 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 and 10 mg intranasal diazepam doses of their investigational formulation with a 5 mg dose of diazepam solution intravenously. Following the 5 and 10 mg doses, the median $t_{max}$ were 20 and 30 minutes respectively and the mean $C_{max}$ were 134.3 ± 62 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 United States 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 United States 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.

The purpose of this study is to assess the long-term safety of NRL-1.

## 2.0 PURPOSE AND STUDY OBJECTIVES

### 2.1 Purpose

The purpose of this study is to assess the safety of repeat intranasal doses of NRL-1administered to Epilepsy subjects.

### 2.2 Study Objectives

#### 2.2.1 Primary Objective

The primary objective of this study is to assess the safety of diazepam after repeat intranasal doses of NRL-1 administered to Epilepsy subjects who experience frequent breakthrough seizures or Acute Repetitive Seizures, over a 12-month period.

#### 2.2.2 Secondary Objectives

The secondary objectives of this study include:

- To assess the tolerability of diazepam after repeat intranasal administration of NRL-1;
- To assess the ability of caregivers to administer NRL-1 based on the Directions for Use (DFU) (see APPENDIX E);
- To assess an improvement in the Quality of Life with NRL-1 use as compared to Diastat.

### 2.3 Description of Study Design

This is a Phase 3, repeat dose, open-label, safety study in Epilepsy subjects who have frequent breakthrough seizures or ARS. NRL-1 will be administered as needed to treat bouts of those seizures over a 12-month period of time. Doses will be defined as 5 mg, 10 mg, 15 mg, or 20 mg based on the subject's body weight. The dosage may be increased or decreased for efficacy or safety reasons, if determined by the Principal Investigator that a different dose is necessary and there is no safety concern. A diary will be used to record the seizure and NRL-1 administration.

The study consists of a screening phase, a baseline, a 12-month treatment period and a follow-up telephone contact 28-days after the last dose of NRL-1 or study termination. The primary purpose of this study is to assess the safety of repeat doses of NRL-1 as intermittent chronic therapy to treat frequent break through seizures or ARS. Subjects will return to the site per the Schedule of Events with all study visits having a ± 7-day window around visits.

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 pediatric), Nasal Examination and Irritation Assessment (The following will be assessed on separate scales: nasal irritation, nasal discharge, mucosal erythema, mucosal edema, mucosal crusting and mucosal epistaxis), Sedation Score Assessment, and Smell Test (NIH Toolbox Odor Identification Test, (1, 2) will be conducted at each visit. A targeted physical examination may be used to evaluate any potentially related side effects.

Subjects and caregivers will be trained on the proper use of the NRL-1 nasal sprayer at screening period and as needed during treatment period. The ability of caregivers to administer NRL-1 based on the DFU will be assessed (see APPENDIX E).

The Quality of Life in Epilepsy (QOLIE) questionnaire will be administered to assess the quality of life while on NRL-1 compared to baseline therapy at time of enrollment. If under the age of 11, no Quality of Life questionnaire will be administered.

Naïve subjects may be entered into this study as well as those subjects completing the protocol DIAZ.001.04 are eligible for the long-term safety study (DIAZ.01.05) and may receive treatment with NRL-1 under DIAZ.01.05 protocol.

## 2.4 Study Endpoints

### 2.4.1 Primary Endpoint

The primary endpoint of this study is safety of NRL-1. There are no efficacy measures evaluated in this study.

### 2.4.2 Secondary Endpoints

The secondary endpoints in this study include:

- Assessment of the tolerability of diazepam after repeat intranasal administration of NRL-1
- Assessment of the ability of caregivers to administer NRL-1 based on the DFU
- Assessment of improvement in the Quality of Life with NRL-1 use as compared to Diastat

### 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

An initial 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).

A second dose may be administered if needed 4-12 hours after the initial dose of NRL-1. Additionally, the dosage may be increased or decreased for efficacy or safety reasons, if determined by the Principal Investigator that a different dose is necessary and there is no safety concern.

### 2.5.3 Bioanalytical Method

Bioanalytical methods will not be used in this study.

## 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 final follow-up telephone contact.

## 2.7 Procedures for Monitoring Subject Compliance

NRL-1 will be administered as needed to treat bouts of those seizures over a 12-month period of time. A diary will be used to record the seizure and NRL-1 administration. At each visit, the seizure and dosing information from the diary including the time when the seizure occurs, when it ended, the dose, and date and time of dosing will be recorded to case report form (CRF).

# 3.0 STUDY POPULATION

The study population will be subjects with a clinical diagnosis of frequent break through seizures or ARS with bouts of uncontrolled seizures, who, in the opinion of the Investigator, may need a benzodiazepine for seizure control.

## 3.1 Inclusion Criteria

Subjects must meet **All** of the following inclusion criteria to be enrolled in this study:

1. Male and female subjects between the ages of 6 and 65 years, inclusive.

2. Written informed consent to participate in the study.

3. Subject has a clinical diagnosis of Epilepsy and while on a stable regimen of anti-epileptic medication, still experiences bouts of seizures (e.g. frequent break through seizures or ARS), and who, in the opinion of the Investigator, may need benzodiazepine intervention for seizure control 1 time every other month on average (i.e. average 6 times a year).

4. Subject has a qualified caregiver or medical professional available that can administer study medication in the event of a seizure.

5. Subjects having either partial or generalized Epilepsy with motor seizures or seizures with clear alteration of awareness.

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). Subjects must have used the same method for at least one (1) month prior to starting the study.

7. No clinically significant abnormal findings in the medical history, on the physical examination or electrocardiogram (QTcF < 450 msec for males and QTcF < 470 msec for females).

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. A history of clinically significant gastrointestinal, renal, hepatic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject.

2. Subject has had significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening.

3. Subjects with active major depression or a past suicide attempt, or any Suicidal Ideation of 3, 4, or 5 or any Suicidal Behavior in Lifetime using C-SSRS. The pediatric C-SSRS should be used for subjects ages 6 to 11. The adult C-SSRS should be used for subjects 12 and greater years of age.

4. A history of allergic or adverse responses to diazepam or any comparable or similar product.

5. Participation in a clinical trial other than protocol DIAZ.001.04 within 30 days prior to Day 0. Participation in an observational (non-interventional) study is not excluded as long as there are no scheduling conflicts with this study.

6. Positive serum pregnancy test (ß-hCG) at screening for subjects age 12 years or greater.

7. Positive blood screen for Human immunodeficiency virus (HIV), Hepatitis B surface antigen (HbSAg), or Hepatitis C, or a positive urine screen for alcohol, or drugs of abuse except marijuana use for medical reasons. 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.

## 4.0 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 and followed up during the treatment period and until follow-up telephone contacts.

Any AE reported by the subject or noted by the Investigator or his/her designee will be recorded on the CRF regardless of the Investigator opinion of causality. Events that occur after dosing in a home setting will be recorded in a diary and reported at the next study visit. 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, 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.

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 screening 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, Alcohol, and Tobacco Screen

Urine samples will be collected at screening for amphetamines, barbiturates, cocaine metabolites, methadone, opiate metabolites, phencyclidine, marijuana metabolites, and alcohol. 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 for medical reasons should be entered in the CRF page for concomitant medication.

### 4.2.5 Other Blood Tests

The presence of human immunodeficiency virus (HIV) antibody, Hepatitis B surface antigen (HbSAg), and Hepatitis C antibody will be assessed at screening.

## 4.3 Physical Examinations and Medical History

### 4.3.1 Physical and Neurological Examination

The Investigator or designee will perform a physical and neurological examination at screening and Day 365. Targeted physical examination may be used during the treatment period to assess potentially related adverse events. 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.). C-SSRS will be used to document suicidality at Screening in order to classify suicidal events.

## 4.4 C-SSRS

The C-SSRS, a measure of suicidal ideation and behavior, will be used to document suicidality at Screening in order to classify suicidal events and on Days 150 and 365 using the C-SSRS. For adults, screening assessments will use the **Baseline/Screening** version of the C-SSRS. The **Since Last Visit** version of the C-SSRS will be used for post-dosing assessments. For children age 6 to 11 years old, screening assessments will use Children's **Baseline/Screening** version and Children's **Since Last Visit** version will be used for post-dosing assessments.

## 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.

**All ECGs are obtained in triplicate**. Three consecutive ECGs (each approximately 1-2 minutes apart) are performed.

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. 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. Body weight will be measured in kg. Assessments of height and weight will be recorded on the CRF.

### 4.7 Vital Signs

Vital signs (temperature, pulse, respiratory rate, and blood pressure) are to be obtained at screening, baseline, and at each visit during the treatment period. Vital signs will be recorded on the CRF.

### 4.8 Smell Test

Smell tests will be conducted at baseline and at each study visit. The NIH Toolbox for Odor Identification Test will be used for smell tests (1, 2).

### 4.9 Nasal Irritation Assessments

Nasal irritation will be assessed at baseline and each study visit based on the following scales outlined in Section 4.9.1 through 4.9.6 below.

#### 4.9.1 Assessment of Nasal Irritation:

Objective evaluations of nasal irritation will be assessed at baseline and each study visit 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 subjects will also be required to report any incident of bleeding or inflammation in-between the actual evaluation time points.

### 4.9.2 Assessment of Mucosal Erythema:

Objective evaluations of mucosal erythema will be assessed at baseline and at each study visit using the following 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)

### 4.9.3 Assessment of Mucosal Edema:

Objective evaluations of mucosal edema will be assessed at baseline and at each study visit 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

### 4.9.4 Assessment of Nasal Discharge:

Objective evaluations of nasal discharge will be assessed at baseline and at each study visit 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

### 4.9.5 Assessment of Mucosal Crusting:

Objective evaluations of mucosal crusting will be assessed at baseline and at each study visit 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

### 4.9.6 Assessment of Mucosal Epistaxis:

Objective evaluations of mucosal epistaxis will be assessed at baseline and at each study visit 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

## 4.10 Quality of Life questionnaire

The QOLIE questionnaire will be administered to assess the quality of life while on NRL-1 compared to baseline therapy at time of enrollment (see APPENDIX D). QOLIE-AD-48 will be used for subjects age 11-18 years of with epilepsy. Subjects age 18 years or older should complete the QOLIE-31-P (APPENDIX D). If under the age of 11, no Quality of Life questionnaire will be administered.

## 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 and at each visit during the treatment period. Please note that subjects age 6 to 11 are not required to take a pregnancy test. If a serum pregnancy test is done on Day -1, urine pregnancy test does not have to be repeated if done within 72 hours of study initiation (baseline).

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

No pharmacokinetic measures will be assessed during this trial.

# 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. Subjects will return to the site per the Schedule of Events with all study visits having a ± 7-day window around visits.

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-specific 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 prior to Day 0. Screening evaluations performed within 24 hours (Day -1 to Day 0) of dosing do not need to be repeated.

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. The screening assessment will use the Baseline/Screening version of the C-SSRS. If the subject reports a history of major depression or a past suicide attempt, she/he is not eligible for the study. The pediatric 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.
- Physical and neurological examination, including height and weight measurements.
- Vital signs consisting of temperature, blood pressure, respiratory rate, and pulse.
- 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)
- Subject/caregiver training

### 8.3 Baseline Evaluations (Day -3 to 0, pre-dose)

Baseline assessments include the followings:

- Review of the inclusion/exclusion criteria and medical history (including seizure history)
- Any restricted concomitant medications
- Weight
- Vital signs consisting of temperature, respiratory rate, blood pressure, and pulse
- Urine sample for pregnancy test. If a serum pregnancy test is done on Day -1, urine pregnancy test does not have to be repeated if done within 72 hours of study initiation (baseline)
- 12-lead ECGs
- Assessment of the ability of caregivers to administer NRL-1
- Quality of Life questionnaire. If under the age of 11, no Quality of Life questionnaire will be administered.
- Smell Test (1, 2)

- Nasal examination and irritation assessments (The following will be assessed on separate scales: nasal irritation, nasal discharge, mucosal erythema, mucosal edema, mucosal crusting and mucosal epistaxis)
- Diary to record seizure and NRL-1 administration
- AE assessment

### 8.4 Drug Administration

The calendar date and 24-hour clock time of all doses will be recorded on the CRF. A second dose may be administered if needed 4-12 hours after the initial dose of NRL-1.

### 8.5 Day 30 to 330 (± 7 days)

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

- Vital signs consisting of temperature, blood pressure, respiratory rate, and pulse
- C-SSRS. The pediatric 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.
- Hematology, Serum Chemistry and Urinalysis
- Urine pregnancy test
- Smell Test (1, 2)
- Nasal examination and irritation assessments (The following will be assessed on separate scales: nasal irritation, nasal discharge, mucosal erythema, mucosal edema, mucosal crusting and mucosal epistaxis)
- Concomitant medications
- AEs
- Assessment of the ability of caregivers to administer NRL-1
- Quality of Life questionnaire. If under the age of 11, no Quality of Life questionnaire will be administered.
- Diary to record seizure and NRL-1 administration

### 8.6 Day 365 (± 7 days)

Assessments on Day 365 include the followings:

- Physical and neurological examination including height and weight
- Vital signs consisting of temperature, blood pressure, respiratory rate, and pulse

- C-SSRS. The pediatric 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.
- Hematology, Serum Chemistry and Urinalysis
- Urine pregnancy test
- Smell Test (1, 2)
- Nasal examination and irritation assessments (The following will be assessed on separate scales: nasal irritation, nasal discharge, mucosal erythema, mucosal edema, mucosal crusting and epistaxis)
- Concomitant medications
- AEs
- Assessment of the ability of caregivers to administer NRL-1
- Quality of Life questionnaire. If under the age of 11, no Quality of Life questionnaire will be administered.
- Diary to record seizure and NRL-1 administration

### 8.7 Treatment beyond Day 365

Subjects may continue treatment on NRL-1 after the primary study period on Day 365 at the discretion of the investigator, and until discontinuation of the DIAZ.001.05 study by the Sponsor. For treatment beyond Day 365, it is recommended that subjects are contacted by the Investigator at least each 3 months to obtain information on any adverse events. Study visits after Day 365 for safety assessment will be recorded in the EDC (CRF) as Unscheduled visits.

### 8.8 Follow Up telephone contact

Follow-up phone calls 28 days (± 3 days) after the last dose of NRL-1 dosing to determine if any AE has occurred and to follow-up on any TEAE(s) ongoing since last communication with the subject and concomitant medications.

### 8.9 Termination Procedures

At early termination, all subjects will be contacted by phone calls approximately 7 days (± 2 days) after the subject withdrew the study or after the final dose of NRL-1. Subject will be followed up for AEs and concomitant medications.

## 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 experience pregnancy
- Potential suicide attempt assessed by C-SSRS and/or Investigator's assessment
- 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 dispensing to study staff responsible for administration to study subjects and reconciliation will occur after dosing.

## 10.5 Administration of Study Drug

Dosing will be according to the following procedure:

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).

A second dose may be administered if needed 4-12 hours after the initial dose of NRL-1. Additionally, the dosage may be increased or decreased for efficacy or safety reasons, if determined by the Principal Investigator that a different dose is necessary and there is no safety concern.

### 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 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 AEs starts on Day 0 after the baseline assessment is completed and ends 28-days (± 3-days) after study termination by telephone contact.

If an AE remains unresolved at final follow-up telephone contact, the subject may 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, for 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 maybe 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. |
| 2 | Moderate | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. |

| CTCAE Grade | Common Term | Description |
|---|---|---|
| 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 (GCP) (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

Up to 100 subjects, at least 30 age 6 to 11 years and up to 70 over 12 years of age, are to be enrolled.

### 12.2 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 vital signs and change from screening for clinical laboratory tests (serum chemistry, hematology, and urinalysis).

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, nasal discharge, mucosal erythema, mucosal edema, mucosal crusting and

mucosal epistaxis. Nasal irritation will be assessed at baseline and each study visit as well as based on reports of any nasal mucosal adverse events between visits to the clinical site

AE collection will begin on Day 0 after baseline assessments are complete prior to the initial treatment with NRL-1 and continue for 28-days after Day 365. AEs 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. AEs that occur after dosing in a home setting will be recorded in a diary and reported at the next study visit. Subjects will receive follow-up telephone contact approximately 28 days (± 3 days) after Day 365 to determine if any AE has occurred and to follow-up on any TEAEs ongoing since last communication with the subject.

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.

Smell tests will be conducted at baseline and at each study visit. The NIH Toolbox for Odor Identification Test will be used as smell tests (1, 2).

The C-SSRS for adults and pediatrics, a measure of suicidal ideation and behavior, will be used to document suicidality in order to classify suicidal events. Suicidality will be assessed at screening for eligibility. The pediatric 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 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.

# 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 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 standard operating procedure (SOP) 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 100% source verified against corresponding source documentation (e.g., office and clinical laboratory records) for each subject. 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 U.S. 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 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 Procedure

| **Study Procedure** | **Screening[a]** | **Baseline[b]** | **Treatment period and Visit Days** | | | | | | | | **Follow Up telephone contact[c]** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -21 to Day -1** | **Day -3 to Day 0** | **Day 30[d]** | **Day 90[d]** | **Day 150[d]** | **Day 210[d]** | **Day 270[d]** | **Day 330[d]** | **Day 365[d]** | **Day >365[e]** | **28 Days after Termination** |
| Signed informed consent | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | | | | |
| Medical history including seizure history | X | X | | | | | | | | | |
| Columbia-Suicide Severity Rating Scale (C-SSRS)[f] | X | | | | X | | | | X | | |
| Physical and Neurologicalexam (including HEENT)[g] | X | | | | | | | | X | | |
| Vital signs[h] | X | X | X | X | X | X | X | X | X | | |
| Height and Weight | X | X[i] | | | | | | | X | | |
| Hematology, Serum Chemistry and Urinalysis | X | | | | X | | X | | X | | |
| Serum or urine ß-hCG (Pregnancy)[j] | X | X | X | X | X | X | X | X | X | | |
| HIV Antibody and Hepatitis Test[k] | X | | | | | | | | | | |
| Urine Drug and AlcoholScreen[l] | X | | | | | | | | | | |
| Prior and Concomitant medication assessment | X | X | X----------→ | | | | | | | | X |
| Adverse event assessment[m] | | X | X----------→ | | | | | | | | X |
| ECG (12-Lead in triplicate)[n] | X | X | | | | | | | | | |
| Smell Test[o] | | X | X | X | X | X | X | X | X | | |
| Assessment of the ability of caregivers to administer NRL-1[p] | | X | X | | X | | X | | X | | |
| Nasal Examination and Irritation Assessment[q] | | X | X | X | X | X | X | X | X | | |
| Quality of Life in Epilepsy questionnaire (QOLIE)[r] | | X | X | | X | | X | | X | | |
| **NRL-1 Dispensed[s]** | | X | X----------→ | | | | | | | | |
| Diary to record seizure and NRL-1 administration | | X | X----------→ | | | | | | | | |
| Subject/caregiver training[t] | X | | X----------→ | | | | | | | | |

a. Screening evaluations must be performed within 21 days prior to dosing on Day 0. Screening evaluations performed within 24 hours (Day -1 to Day 0) of dosing do not need to be repeated.
b. Baseline evaluations will be performed within 72 hours prior to study initiation on Day 0. Baseline assessment may be conducted at clinic.
c. Subjects will receive follow-up telephone contact approximately 28 days (± 3 days) after study termination.
d. Study window at visits from Days 30 to 365 is ± 7 days.
e. Subjects that continue on therapy after Day 365 should be contacted to solicit information on potential adverse events at least each 3 months. Any site visits for standard of care evaluations should be recorded in the EDC (CRF) as Unscheduled visits.
f. C-SSRS, a measure of suicidal ideation and behavior, will be used to document suicidality in order to classify suicidal events. The pediatric 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 (see APPENDIX B).
g. Targeted physical examinations may be used during the treatment period to evaluate potentially related adverse events.
h. Vital signs (temperature, pulse, respiratory rate, and blood pressure) are to be obtained.
i. Weight only.

j. A serum (ß-hCG) pregnancy test will be administered to females of childbearing potential at screening. Pregnancy test will be done with urine at baseline and at the visits during the treatment period. If a serum pregnancy test is done on Day -1, urine pregnancy test does not have to be repeated if done within 72 hours of study initiation (baseline).
k. Hepatitis B surface antigen (HbSAg), or Hepatitis C
l. When marijuana is 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.
m. Adverse event assessment is continuous from Day 0 after baseline assessments are complete. Events that occur after dosing in a home setting will be recorded in a diary and reported at the next study visit.
n. ECG is to be performed in triplicate. Three consecutive ECGs (each approximately 1-2 minutes apart) are performed.
o. Smell tests will be conducted at baseline and at each visit. The NIH Toolbox Odor Identification Test will be used as smell tests.
p. Ability of caregivers to administer NRL-1 will be assessed.
q. Nasal examination and scoring for nasal irritation, mucosal erythema, mucosal edema, nasal discharge, mucosal crusting and mucosal epistaxis will be performed at baseline and at each site visit.
r. QOLIE questionnaire will be administered to assess the quality of life while on NRL-1 compared to baseline therapy at time of enrollment (see APPENDIX D ). If under the age of 11, no Quality of Life questionnaire will be administered.
s. NRL-1 may be dispensed to treat bouts of uncontrolled seizures (frequent break through seizures or ARS) after baseline procedures completed. The amount of drug dispensed is dependent on the investigators judgment and anticipated need of the subjects to cover the period between study visits, but should not exceed the amount needed to treat 5 seizure episodes a month.
t. Subjects and caregivers will be trained based on the Direction for Use (DFU) for the proper use of the NRL-1 nasal sprayer. Training may be given as needed during the treatment period. Primary caregivers who are trained may train other secondary caregivers.

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

## APPENDIX B: 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. For adults, screening assessments will use the **Baseline/Screening** version of the C-SSRS. The **Since Last Visit** version of the C-SSRS will be used for post-dosing assessments. For children age 6 to 11, screening assessments will use Children's **Baseline/Screening** version 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<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 | ____ | ____ |

| ***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><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

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.* | 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 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)* | 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>***Have you made a suicide attempt?***<br>***Have you done anything to harm yourself?***<br><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

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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>***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 <u>do anything</u> 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, <u>not at all</u> 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: | Yes ☐ No ☐<br><br>Total # of Attempts<br>_____ |
| **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | Yes ☐ No ☐ |
| **Has subject engaged in Self-Injurious Behavior, intent unknown?** | Yes ☐ No ☐ |
| **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>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>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 ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | Yes ☐ No ☐ |

| *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)

## Children's Since Last Visit Version

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.* | **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><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>☐ ☐ |

| *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><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>_____ |

# APPENDIX C: 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 D: QUALITY OF LIFE IN EPILEPSY (QOLIE)

Quality of Life in Epilepsy will be administered to assess the quality of life while on NRL-1 compared to baseline therapy at time of enrollment. QOLIE-AD-48 will be used for subjects age 11-18 years with epilepsy. Subjects age 18 years or older should complete the QOLIE-31-P. If under the age of 11, no Quality of Life questionnaire will be administered.

## Quality of Life in Epilepsy for Adolescents: QOLIE-AD-48 (Version 1)



**Today's Date** ___/___/___

**Name:** _____

### INSTRUCTIONS

The QOLIE-AD-48 is a survey of health-related quality of life for adolescents (11-18 years of age) with epilepsy. Adults (18 years or older) should complete the QOLIE-31-P, designed for that age group. This questionnaire should be completed only by the person who has epilepsy (not a relative or friend) because no one else knows how YOU feel.

There are 48 questions (in two parts) about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3...). The first part asks about your general health. The second part asks about the effects of your epilepsy and antiepileptic medications. **Please answer every question** by circling the appropriate number (1, 2, 3, 4, 5). If you are not sure about how to answer a question, please give the **best answer you can**. You may write notes in the margin to explain your feelings. Even if some questions look similar, answer every question.

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation on the side of the page. These notes may be useful if you discuss the QOLIE-AD-48 with your doctor. Completing the QOLIE-AD-48 before and after treatment changes may help you and your doctor understand how the changes have affected your life.

*This copy of the QOLIE-AD-48 is provided by www.epilepsy.com, your source for epilepsy information, and the QOLIE Development Group. We wish you success in living your life with epilepsy!*

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### PART 1: GENERAL HEALTH

1. In general, would you say your health is: *(Circle one number)*

| Excellent | Very good | Good | Fair | Poor |
|---|---|---|---|---|
| 5 | 4 | 3 | 2 | 1 |

---

2. **Compared to 1 year ago,** how would you rate your health in general **now?**

| Much better now | Somewhat better now | About the same now | Somewhat worse now | Much worse now |
|---|---|---|---|---|
| 5 | 4 | 3 | 2 | 1 |

---

The following questions are about activities you might do during a TYPICAL DAY. We want you to answer how much **your health** limits you in these activities. *(Circle one number on each line)*

| In the past 4 weeks, how often has your health limited: | Very often | Often | Some-times | Not often | Never |
|---|---|---|---|---|---|
| 3. Heavy activities, such as running, participating in very active sports (such as gymnastics, rollerblading, skiing)? | 1 | 2 | 3 | 4 | 5 |
| 4. Moderate activities (such as walking to school, bicycle riding)? | 1 | 2 | 3 | 4 | 5 |
| 5. Light activities (such as carrying packages or a school bag full of books)? | 1 | 2 | 3 | 4 | 5 |
| 6. Other daily activities (such as taking a bath/shower alone, going to and from school alone)? | 1 | 2 | 3 | 4 | 5 |

The following questions are about your regular daily activities, such as chores at home, baby-sitting, attending school, being with friends and family, doing homework, or taking part in after-school activities and lessons. We want to know if you had any of the following difficulties with your regular activities as a result of any **physical problems (such as illness) or emotional problems (such as feeling sad or nervous)?**

| In the past 4 weeks, how often have physical or emotional problems caused you to: | Very often | Often | Some-times | Not often | Never |
|---|---|---|---|---|---|
| 7. Do fewer things than you would have liked to do? | 1 | 2 | 3 | 4 | 5 |
| 8. Limit the ***kind*** of schoolwork, chores, sports, or other activities you did? | 1 | 2 | 3 | 4 | 5 |
| 9. Have ***difficulty*** performing the schoolwork, chores, sports, or other activities you did (for example, it took extra effort) ? | 1 | 2 | 3 | 4 | 5 |

| In the past 4 weeks, how often: | Very often | Often | Some-times | Not often | Never |
|---|---|---|---|---|---|
| 10. Did you skip school for no reason? | 1 | 2 | 3 | 4 | 5 |
| 11. Were you in trouble in school (with teachers or other staff)? | 1 | 2 | 3 | 4 | 5 |

| | Very often | Often | Some-times | Not often | Never |
|---|---|---|---|---|---|
| 12. Were you in trouble out of school (with police, security guards, bus driver, etc)? | 1 | 2 | 3 | 4 | 5 |

These questions are about how you FEEL and how things have been for you during **the past 4 weeks.** For each question, please indicate the one answer that comes closest to the way you have been feeling. *(Circle one number on each line)*

| In the past 4 weeks, how often have you: | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| 13. Had trouble concentrating on an activity? | 1 | 2 | 3 | 4 | 5 |
| 14. Had trouble concentrating on reading? | 1 | 2 | 3 | 4 | 5 |

The following questions are about mental activities and language problems that may interfere with your normal schoolwork or living activities. *(Circle one number on each line)*

| past 4 weeks, how often have you: | All of the time | Most of the time | Some of the time | A little of the time | None of the timeinthe |
|---|---|---|---|---|---|
| 15. Had difficulty thinking? | 1 | 2 | 3 | 4 | 5 |
| 16. Had difficulty figuring out and solving problems (such as making plans, making decisions, learning new things)? | 1 | 2 | 3 | 4 | 5 |
| 17. Had a problem with complicated projects that require organization or planning like computer games or difficult homework)? | 1 | 2 | 3 | 4 | 5 |
| 18. Had trouble remembering things you read hours or days before? | 1 | 2 | 3 | 4 | 5 |
| 19. Had trouble finding the correct word? | 1 | 2 | 3 | 4 | 5 |
| 20. Had trouble understanding your teachers? | 1 | 2 | 3 | 4 | 5 |
| 21. Had trouble understanding what you read? | 1 | 2 | 3 | 4 | 5 |

The following questions ask about the support you get from others (including family and friends).
*(Circle one number on each line)*

| In the past 4 weeks, how often did you: | Very Often | Often | Some-times | Not often | Never |
|---|---|---|---|---|---|
| 22. Have someone available to help you if you needed and wanted help? | 5 | 4 | 3 | 2 | 1 |
| 23. Have someone you could confide in or talk to about things that were troubling you? | 5 | 4 | 3 | 2 | 1 |
| 24. Have someone you could talk to when you were confused and needed to sort things out? | 5 | 4 | 3 | 2 | 1 |
| 25. Have someone who accepted you as you were, both your good points and bad points? | 5 | 4 | 3 | 2 | 1 |

**PART 2: EFFECTS OF EPILEPSY AND ANTIEPILEPSY MEDICATIONS**

The following questions ask about how your epilepsy or medications (antiepileptic drugs) have affected your life in the past 4 weeks. *(Circle one number on each line)*

| In the past 4 weeks, how often did you: | Very Often | Often | Some-times | Not often | Never |
|---|---|---|---|---|---|
| 26. Feel that **epilepsy or medications** limited your social activities (such as hanging out with friends, doing extra-curricular activities)compared with social activities of others your age? | 1 | 2 | 3 | 4 | 5 |
| 27. Feel alone and isolated from others because of your epilepsy/seizures ? | 1 | 2 | 3 | 4 | 5 |
| 28. Miss classes because of seizures or medications? | 1 | 2 | 3 | 4 | 5 |
| 29. Use epilepsy or medication side effects as an excuse to avoid doing something you didn't really want to do? | 1 | 2 | 3 | 4 | 5 |
| 30. Feel embarrassed or "different" because you had to take medications? | 1 | 2 | 3 | 4 | 5 |
| 31. Feel that epilepsy or medications limited your school performance? | 1 | 2 | 3 | 4 | 5 |
| 32. Feel you had limitations because of your seizures? | 1 | 2 | 3 | 4 | 5 |
| 33. Feel that epilepsy or medications limited your independence? | 1 | 2 | 3 | 4 | 5 |
| 34. Feel that epilepsy or medications limited your social life or dating? | 1 | 2 | 3 | 4 | 5 |
| 35. Feel that epilepsy or medications limited your participation in sports or physical activities? | 1 | 2 | 3 | 4 | 5 |

The following question asks about possible side effects from antiepileptic drugs.
*(Circle one number on each line)*

| In the past 4 weeks, how did you feel: | Very Bad | Bad | OK | Good | Very good |
|---|---|---|---|---|---|
| 36. About how you looked (side effects such as weight gain, acne/pimples, hair change, etc.)? | 1 | 2 | 3 | 4 | 5 |

| In the past 4 weeks, how much were you bothered by: | A Lot | Some | Not much | A little | Not at all |
|---|---|---|---|---|---|
| 37. Limits set by parents/family because of your epilepsy or medications? | 1 | 2 | 3 | 4 | 5 |

Next are some statements people with epilepsy sometimes make about themselves. For each statement, circle the answer that comes closest to the way **you** have felt about **yourself** in the **past 4 weeks.** *(Circle one number on each line)*

| | Strongly agree | Agree | Disagree | Strongly disagree |
|---|---|---|---|---|
| 38. I consider myself to be less than perfect because I have epilepsy. | 1 | 2 | 3 | 4 |
| 39. If I applied for a job, and someone else also applied who didn't have epilepsy, the employer should hire the other person. | 1 | 2 | 3 | 4 |
| 40. I can understand why someone wouldn't want to date me because I have epilepsy. | 1 | 2 | 3 | 4 |
| 41. I don't blame people for being afraid of me because I have epilepsy. | 1 | 2 | 3 | 4 |
| 42. I don't blame people for taking my opinions less seriously than they would if I didn't have epilepsy. | 1 | 2 | 3 | 4 |
| 43. I feel that my epilepsy makes me mentally unstable | 1 | 2 | 3 | 4 |

The following questions ask about your attitudes toward epilepsy. Circle one number for how often in the **past 4 weeks** you have had these attitudes. *(Circle one number on each line)*

| | Very bad | A little bad | Not sure | A little good | Very good |
|---|---|---|---|---|---|
| 44. How good or bad has it been that you have epilepsy? | 1 | 2 | 3 | 4 | 5 |

| | Very Unfair | A little unfair | Not sure | A little fair | Very fair |
|---|---|---|---|---|---|
| 45. How fair has it been that you have epilepsy? | 1 | 2 | 3 | 4 | 5 |

| | Very sad | A little sad | Not sure | A little happy | Very happy |
|---|---|---|---|---|---|
| 46. How happy or sad has it been for you to have epilepsy? | 1 | 2 | 3 | 4 | 5 |

| | Very bad | A little bad | Not sure | A little good | Very good |
|---|---|---|---|---|---|
| 47. How bad or good have you felt it is to have epilepsy? | 1 | 2 | 3 | 4 | 5 |

| | Very often | Often | Some-times | Not often | Never |
|---|---|---|---|---|---|
| 48. How often do you feel that your epilepsy kept you from starting new things? | 1 | 2 | 3 | 4 | 5 |

Optional Items:

| In the past 4 weeks, how often did you: | Very often | Often | Some-times | Not often | Never |
|---|---|---|---|---|---|
| Worry about having another seizure? | 1 | 2 | 3 | 4 | 5 |
| Fear dying because of seizures? | 1 | 2 | 3 | 4 | 5 |
| Worry about hurting yourself during a seizure? | 1 | 2 | 3 | 4 | 5 |

**Please check all pages before stopping to be sure that you have answered all the questions.**

## QUALITY OF LIFE IN EPILEPSY – PROBLEMS: QOLIE-31-P *(Version 2)*



Today's Date_____/ _____/_____
mm dd yy

Name _____ Age: ___ ___ years

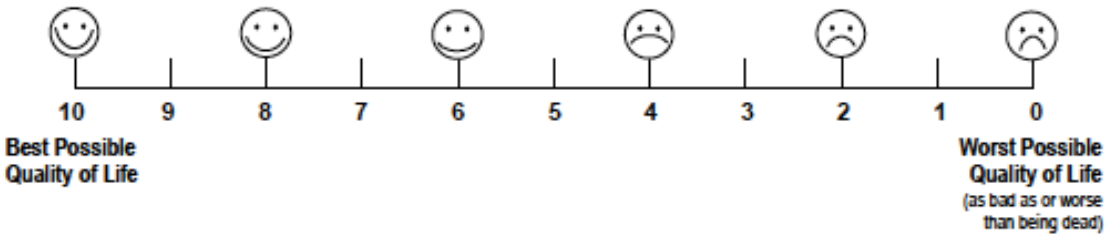
**INSTRUCTIONS**

The QOLIE-31-P is a survey of health-related quality of life for adults (18 years or older) with epilepsy. [Adolescents (ages 11-17 years) should complete the QOLIE-AD-48, designed for that age group.] This version differs from the original QOLIE-31 (version 1) in the addition of questions about how much distress you feel about problems and worries related to epilepsy. This questionnaire should be completed only by the person who has epilepsy (not a relative or friend) because no one else knows how YOU feel.

There are 38 questions about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3...). If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation on the side of the page. These notes may be useful if you discuss the QOLIE-31-P with your doctor. Completing the QOLIE-31-P before and after treatment changes may help you and your doctor understand how the changes have affected your life.

*This copy of the QOLIE-31-P is provided by www.epilepsy.com, your source for epilepsy information, and the QOLIE Development Group. We wish you success in living your life with epilepsy!*

1. Overall, how would you rate your quality of life?
   *(Circle one number on the scale below)*



**Part A.**

*These questions are about how you have been FEELING during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.*

***How much of the time during the past 4 weeks...***

*(Circle one number on each line)*

| | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| 2. Did you feel full of pep? | 1 | 2 | 3 | 4 | 5 | 6 |
| 3. Did you have a lot of energy? | 1 | 2 | 3 | 4 | 5 | 6 |
| 4. Did you feel worn out? | 1 | 2 | 3 | 4 | 5 | 6 |
| 5. Did you feel tired? | 1 | 2 | 3 | 4 | 5 | 6 |

*Reviewing only questions in **Part A**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

*(Circle one number)*

| | Not at all | Somewhat | Moderately | A lot | Very much |
|---|---|---|---|---|---|
| 6. How much do the above problems and worries about <u>energy</u> **distress** you overall? | 1 | 2 | 3 | 4 | 5 |

**Part B.**

*These questions are about how you have been FEELING during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.*

**How much of the time during the past 4 weeks…**
*(Circle one number on each line)*

| | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| 7. Have you been a very nervous person? | 1 | 2 | 3 | 4 | 5 | 6 |
| 8. Have you felt so down in the dumps that nothing could cheer you up? | 1 | 2 | 3 | 4 | 5 | 6 |
| 9. Have you felt calm and peaceful? | 1 | 2 | 3 | 4 | 5 | 6 |
| 10. Have you felt downhearted and blue? | 1 | 2 | 3 | 4 | 5 | 6 |
| 11. Have you been a happy person? | 1 | 2 | 3 | 4 | 5 | 6 |

*Reviewing only questions in **Part B**, consider the overall impact of these issues on your life **in the past 4 weeks.***

*(Circle one number)*

| | Not at all | Somewhat | Moderately | A lot | Very much |
|---|---|---|---|---|---|
| 12. How much do the above problems and worries about <u>emotions</u> distress you overall? | 1 | 2 | 3 | 4 | 5 |

## Part C.

*The following questions are about how you FEEL and about problems you may have with daily ACTIVITIES during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.*

The following question asks about how you FEEL and how things have been going for you.

**How much of the time during the past 4 weeks…**

*(Circle one number)*

| | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| 13. Has your health limited your social activities (such as visiting with friends or close relatives)? | 1 | 2 | 3 | 4 | 5 | 6 |

The following questions ask about problems you may have with certain ACTIVITIES.

**How much of the time during the past 4 weeks your epilepsy or antiepileptic medication has caused trouble with…**

*(Circle one number on each line)*

| | A great deal | A lot | Somewhat | Only a little | Not at all |
|---|---|---|---|---|---|
| 14. Leisure activities (such as hobbies, going out) | 1 | 2 | 3 | 4 | 5 |
| 15. Driving (or transportation) | 1 | 2 | 3 | 4 | 5 |

| | Not at all bothersome | | | | Extremely bothersome |
|---|---|---|---|---|---|
| 16. How much do your work limitations bother you? | 1 | 2 | 3 | 4 | 5 |
| 17. How much do your social limitations bother you? | 1 | 2 | 3 | 4 | 5 |

*Reviewing only questions in **Part C**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

*(Circle one number)*

| | Not at all | Somewhat | Moderately | A lot | Very much |
|---|---|---|---|---|---|
| 18. How much do the above problems and worries about <u>daily activities</u> **distress** you overall? | 1 | 2 | 3 | 4 | 5 |

## Part D.

*These questions are about thinking, reading, concentrating and memory problems you may have had during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.*

***How much of the time during the past 4 weeks...***

| *(Circle one number)* | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| 19. Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)? | 1 | 2 | 3 | 4 | 5 | 6 |

| | Yes, a great deal | Yes, somewhat | Only A little | No, not at all |
|---|---|---|---|---|
| 20. In the past 4 weeks, have you had any trouble with your memory? | 1 | 2 | 3 | 4 |

***In the past 4 weeks, how often have you had...***

| *(Circle one number on each line)* | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| 21. Trouble remembering things people tell you? | 1 | 2 | 3 | 4 | 5 | 6 |
| 22. Trouble concentrating on reading? | 1 | 2 | 3 | 4 | 5 | 6 |
| 23. Trouble concentrating on doing one thing at a time? | 1 | 2 | 3 | 4 | 5 | 6 |

| | Not at all bothersome | | | | Extremely bothersome |
|---|---|---|---|---|---|
| 24. How much do your memory difficulties bother you? | 1 | 2 | 3 | 4 | 5 |

*Reviewing only questions in Part D, consider the overall impact of these issues on your life in the past 4 weeks.*

*(Circle one number)*

| | Not at all | Somewhat | Moderately | A lot | Very much |
|---|---|---|---|---|---|
| 25. How much do the above problems and worries about mental function distress you overall? | 1 | 2 | 3 | 4 | 5 |

**Part E.**

*These questions are about problems you may have related to your epilepsy or antiepileptic medication.*

**During the past 4 weeks…**

*(Circle one number on each line)*

| | Not at all bothersome | | | | Extremely bothersome |
|---|---|---|---|---|---|
| 26. How much do physical effects of antiepileptic medication bother you? | 1 | 2 | 3 | 4 | 5 |
| 27. How much do mental effects of antiepileptic medication bother you? | 1 | 2 | 3 | 4 | 5 |

| | Very worried | Somewhat worried | Not very worried | Not worried at all |
|---|---|---|---|---|
| 28. How worried are you that medications you are taking will be bad for you if taken for a long time? | 1 | 2 | 3 | 4 |

*Reviewing only questions in **Part E**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

*(Circle one number)*

| | Not at all | Somewhat | Moderately | A lot | Very much |
|---|---|---|---|---|---|
| 29. How much do the above problems and worries about the <u>effects of medication</u> **distress** you overall? | 1 | 2 | 3 | 4 | 5 |

## Part F.

*These questions are about how you FEEL about your seizures during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.*

**How much of the time during the past 4 weeks…**

| *(Circle one number)* | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| 30. Have you worried about having another seizure? | 1 | 2 | 3 | 4 | 5 | 6 |

| | Very fearful | Somewhat fearful | Not very fearful | Not fearful at all |
|---|---|---|---|---|
| 31. How fearful are you of having a seizure during the next month? | 1 | 2 | 3 | 4 |

| | Worry a lot | Occasionally worry | Don't worry at all |
|---|---|---|---|
| 32. Do you worry about hurting yourself during a seizure? | 1 | 2 | 3 |

| | Very worried | Somewhat worried | Not very worried | Not at all worried |
|---|---|---|---|---|
| 33. How worried are you about embarrassment or other social problems resulting from having a seizure during the next month? | 1 | 2 | 3 | 4 |

| | Not at all bothersome | | | | Extremely bothersome |
|---|---|---|---|---|---|
| 34. How much do your seizures bother you? | 1 | 2 | 3 | 4 | 5 |

*Reviewing only questions in **Part F**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

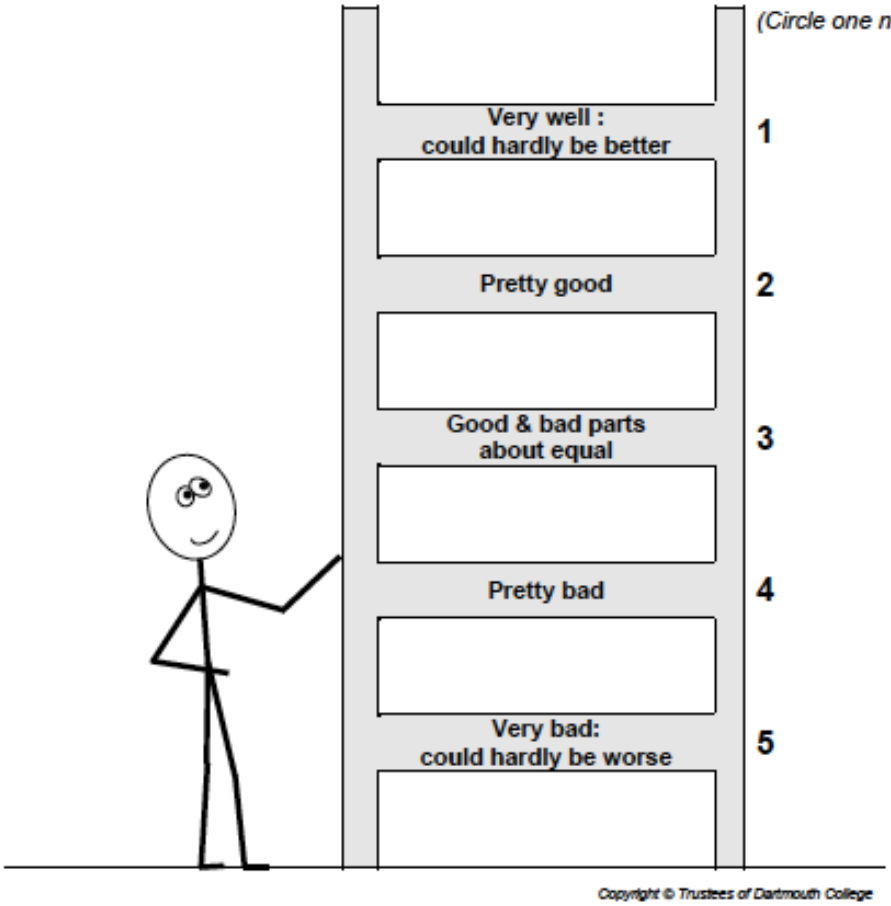
*(Circle one number)*

| | Not at all | Somewhat | Moderately | A lot | Very much |
|---|---|---|---|---|---|
| 35. How much do the above problems and worries about <u>seizures</u> **distress** you overall? | 1 | 2 | 3 | 4 | 5 |

**Part G.**

*The following question asks about how you FEEL about your overall quality of life. Please indicate the one answer that comes closest to the way you have been feeling.*

36. How has the **QUALITY OF YOUR LIFE** been during the **past 4 weeks** (that is, how have things been going for you)?



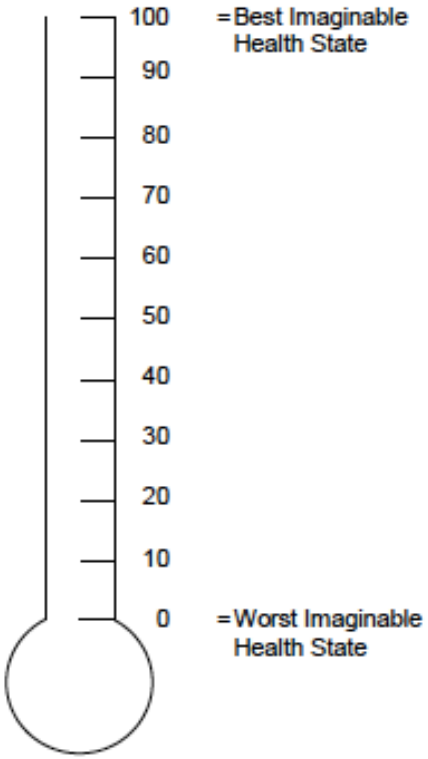

*Reviewing only questions 1 and 36 in Part G (on page 1 and this page), consider the overall impact of your quality of life in the past 4 weeks.*

*(Circle one number)*

| | Not at all | Somewhat | Moderately | A lot | Very much |
|---|---|---|---|---|---|
| 37. How much does the state of your quality of life distress you overall? | 1 | 2 | 3 | 4 | 5 |

**Part H.**

38. How good or bad do you think your HEALTH is?
On the scale below, the best imaginable state of health is 100 and the worst imaginable state is zero (0).
Please indicate how you feel about your health by circling one number on the scale. **Please consider your epilepsy as part of your health when you answer this question.**



**Part I.**

*Considering **ALL** the questions you have answered, please **indicate the areas** related to your epilepsy that are most **IMPORTANT** to you **NOW.***

39. *Number the following topics from '1' to '7', with '1' corresponding to the very most important topic and '7' to the least important one. Please use each number only once.*

- ☐ **A.** Energy (tiredness)
- ☐ **B.** Emotions (mood)
- ☐ **C.** Daily activities (work, driving, social)
- ☐ **D.** Mental activity (thinking, concentrating, memory)
- ☐ **E.** Medication effects (physical, mental)
- ☐ **F.** Seizure worry (impact of seizures)
- ☐ **G.** Overall quality of life

# APPENDIX E: DIRECTIONS FOR USE

# NRL-1 INSTRUCTION GUIDE

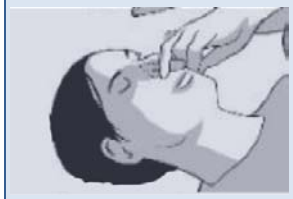
FOR INVESTIGATIONAL USE ONLY. KEEP OUT OF REACH OF CHILDREN.
**IMPORTANT: FOR USE IN THE NOSE ONLY.**
**DO NOT REMOVE OR TEST THE NRL-1 NASAL SPRAYER UNTIL READY TO USE.**

## 1 Identify Seizure Occurrence

**Safely Secure the Person During a Seizure:**

- **Stay Calm**
- **If the person appears to be having a seizure and is standing**, **prevent them from falling** by holding in a hug, or try to help them gently to the floor and lay the person on their side
- **If the person having a seizure is on the ground when you arrive, try to position them on their side** so that any saliva or vomit may leak out of their mouth
- **Move furniture or other objects away** to prevent injury to the person during the seizure

## 2 Give NRL-1 Nasal Spray



**HOLD** the NRL-1 nasal spray with your thumb on the bottom of the nasal spray and your first and middle fingers on either side of the nozzle.

- The person can be in any position to receive a dose of NRL-1 nasal spray


**Gently insert the tip of the nozzle into either nostril.**

- Insert the tip of the nozzle into **one nostril**, until your fingers on either side of the nozzle are against the bottom of the patient's nose

**Press the bottom of the nasal spray firmly** to give the dose of NRL-1 nasal spray.

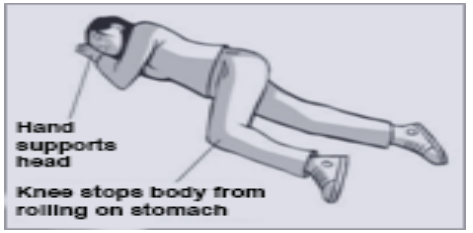
- Remove the NRL-1 nasal spray from the nose

**For 15mg or 20mg dose, repeat with second sprayer in other nostril**

## 3 After the Seizure: Evaluate and Support

**Check the person for injuries.**

**Move the person on their side (recovery position)** if you could not turn the person onto their side during the seizure.




**Loosen tight clothing** and provide a safe area where the person can rest

**Keep the person on their side** and note the time NRL-1 was given and observe

**Your doctor may prescribe an additional dose of NRL-1 spray which may be given 4 hours after the first dose.** Repeat **Step 2** to give another dose of NRL-1 nasal spray.

**Not more than 2 doses per seizure episode. Call 911 if seizure does not subside after second dose of NRL-1. Allow 5 days before repeating dose.**

Neurelis, Inc.
Version Date: 07 JUNE 2016