# CLINICAL TRIAL PROTOCOL

**Title: A Phase 1b dose-finding study of DDFPe in acute ischemic stroke**

**Protocol Number:** NVX-208-AIS

UAMS IRB Number: 205529

**Phase: 1b**


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## Study Summary

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|---|---|
| **Title** | **A Phase 1b dose-finding study of DDFPe in Acute Ischemic Stroke** |
| **Sponsor** | University of Arkansas for Medical Sciences |
| **Protocol Number** | NVX-208-AIS |
| **Phase** | Phase 1b |
| **Methodology** | Randomized, placebo controlled, blinded escalating dose design; 6:2 DDFPe to placebo at each dose level |
| **Rationale** | To provide dosing guidelines for a Phase 2 study in patients who have an acute stroke |
| **Study Duration** | Approximately 18 months |
| **Study Center(s)** | University of Arkansas for Medical Sciences, Little Rock, AR |
| **Primary Objective** | To determine the maximum tolerated dose (MTD) of Dodecafluoropentane emulsion (DDFPe) in subjects with acute ischemic stroke (AIS) |
| **Secondary Objective** | To determine the safety of DDFPe in subjects who have experienced an AIS event |
| **Number of Subjects** | Up to 24 completed subjects |
| **Diagnosis and Main Eligibility Criteria** | ➢ Inclusion: ages 18years old or older, male or female, AIS with NIH Stroke Scale between 2 and 20<br>➢ Exclusion: Severe cerebral hemorrhage or severe hemorrhagic stroke, intracranial surgery or major head trauma within 3 months, > 12 hours since onset of stroke symptoms, clinically significant cardiac or pulmonary disease, current anticoagulant therapy (except low doses of aspirin or low molecular weight heparin), pregnancy or breastfeeding |
| **Study Product, Dose, Route, Regimen** | Dodecafluoropentane emulsion (DDFPe)<br>Dose Range: 0.05, 0.10, and 0.17 mL/kg (Maximum dose: 17 mL/dose)<br>Route: Intravenous over 5-10 minutes every 90 ± 10 minutes x 3 doses<br><br>Placebo - Intralipid® 20% IV fat emulsion<br>Dose: Sterile 1:101 dilution of Intralipid® in aqueous sodium chloride (0.9% w/v)<br>Route: Intravenous over 5-10 minutes every 90 ± 10 minutes x 3 doses |
| **Duration of Administration** | Approximately 3-4 hours |
| **Reference Therapy** | None |
| **Primary Outcome Measures** | DLT (dose limiting adverse events) including clinically significant changes in vital signs, peripheral oxygen saturation (pulse oximetry), clinical symptoms, NIH Stroke Scale, laboratory values, and ECG measurements, Grade 3 or higher scores on selected CTCAE 4 measures |

**ABBREVIATIONS**

| | |
|---|---|
| AE | Adverse Event |
| AIS | Acute ischemic stroke |
| ALT | Alanine Aminotransferase |
| ANOVA | Analysis of Variance |
| aPTT | Activated Partial Thromboplastin Time |
| AST | Aspartate Aminotransferase |
| AUC | Area under the Concentration vs. Time Curve |
| BP | Blood Pressure |
| BUN | Blood Urea Nitrogen |
| CL | Clearance |
| Cmax | Maximum Concentration |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| CT | Computed (Computerized) Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DDFP | Dodecafluoropentane |
| DDFPe | Dodecafluoropentane emulsion |
| DBP | Diastolic Blood Pressure |
| DLT | Dose Limiting Toxicity |
| DSM | Data Safety Monitor |
| ECG | Electrocardiogram |
| FDA | Food and Drug Administration |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | Heart rate |
| IEC | Independent Ethics Committee |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IV | Intravenous |
| LAR | Legally Authorized Representative |
| LFT | Liver Function Tests |
| mmHg | Millimeters of Mercury |
| mRS | modified Rankin Scale |
| mSec | Millisecond |
| MTD | Maximum Tolerated Dose |
| N/A | Not Applicable |
| ND | Not Done |
| NIH | National Institutes of Health |
| NIHSS | National Institutes of Health Stroke Scale |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| NYHA | New York Heart Association |
| OTs | Oxygen Transporters |
| PHI | Personal Health Information |
| PTB | PE-Telomer-B |
| RR | Respiratory Rate |

| | |
|---|---|
| SAE | Serious Adverse Event |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| Tmax | Time at Which the Maximum Concentration (Cmax) Occurs |
| tPA | Tissue Plasminogen Activator |
| Vd | Volume of Distribution |
| UAMS | University of Arkansas for Medical Sciences |
| UPIRTSO | Unanticipated Problem Involving Risk to Subjects or Others |

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## 1.0 Background and Rationale

### 1.1 Background

Stroke is the fifth leading cause of death in the United States and is the leading cause of long term disability[1,2]. Distinct geographic disparities in stroke mortality, with highest rates in the southeast United States including Arkansas, are known as the "stroke belt." There the average stroke mortality is ≈20% to 40% higher than the rest of the nation[3]. Stroke is the leading cause of serious long-term disability[3]. Between 2012 and 2030, disability and medical costs related to stroke are projected to triple, from $71.6 billion to $184.1 billion, with the majority of the projected increase in costs arising from those 65 to 79 years of age[4].

There are two main forms of stroke, ischemic and hemorrhagic. An ischemic stroke occurs in 85% of cases and is caused by cerebral vessel occlusion, obstructing blood flow to a portion of the brain[1]. Currently, the only approved therapies for acute ischemic stroke are IV tissue plasminogen activator (tPA), a thrombolytic agent that clears the thrombus within the blood vessel, or intra-arterial catheter thrombectomy. Despite the availability of therapy, it reaches only approximately 7% of ischemic stroke victims in the United States[5]. Delay beyond the effective time window for therapy is a common reason for failure. To reduce the devastating impact of stroke on individuals and society, we continue to seek ways to improve functional recovery and limit ischemic damage in stroke patients. The potential neuroprotective agent, dodecafluoropentane emulsion (DDFPe) has recently shown strong positive effects in pre-clinical animal models of acute ischemic stroke[6-11]. Other perfluorocarbons have been tested in humans as potential neuroprotectants and blood substitutes[12] yet none have been successful.

DDFPe (2% w/vol) is a liquid perfluorocarbon nanodroplet which transports over 200 times as much oxygen per milligram of fluorocarbon as others tested as oxygen therapeutics[13-15]. It is active at doses that have already been safely tested as bolus IV injections in humans as an ultrasound contrast agent by Sonus Pharmaceutical in over 2200 patients,[16,17] and was approved by the European Medicines Agency as an ultrasound contrast agent. NuvOx Pharma owns these data and the FDA has given NuvOx guidance that the prior human data from the ultrasound contrast development can be used in support of therapeutic development of DDFPe. NuvOx is currently conducting a Phase Ib/II trial of DDFPe as a radiation sensitizer to reverse tumor hypoxia in glioblastoma[18] and is about to start a study in sickle cell disease for which an IND has been granted. NuvOx has received Orphan Drug Designations for both the glioblastoma and sickle cell disease applications.

This fluorocarbon with its greater innate oxygen carrying capacity and smaller particle size that allows delivery to occluded and ischemic areas is a superior oxygen transporter (OT). DDFPe was shown to significantly improve

functional recovery within two hours of dosing and full recovery by 3.5 hours in the rabbit stroke model[6]. A small dose of 0.1 ml/kg was effective in the animal model and may provide clinical neuroprotection during pre-hospital triage and diagnosis[10]. Recent DDFPe studies confirmed its strong capability as a neuroprotectant, which widened the therapeutic window to 9 hours in ischemic stroke rabbit models. In those studies >80% of infarct volume was protected to 24 hours with only 6 doses over the first 9 hours[7].

1.2 Brief Description of the Investigational Product

DDFPe is an emulsion of 2% dodecafluoropentane in stabilizers (sucrose, PE-Telomer B) and phosphate buffered saline (pH 7.0). Compared to higher molecular weight liquid fluorocarbons that have already been studied extensively as OTs, DDFPe carries far more oxygen per gram of fluorocarbon.

Stoichiometrically, DDFP has 200 times the oxygen carrying capacity compared to human hemoglobin. Consequently, if it were administered intravenously (IV) and passed through the lungs of patients breathing high concentrations of oxygen, it would take up large amounts of oxygen and increase the oxygen concentration in blood in a dose-dependent way. Hypothetically, by shifting ischemic environments to normal tissue pO2 environments patient recovery from stroke will be improved.

1.3 Preclinical Studies

Extensive work was done to evaluate the toxicity and PK/PD of DDFPe as an ultrasound contrast-imaging agent. During development, most work was done using "activated" dodecafluoropentane emulsion (DDFPe) referred to as EchoGen® when it was studied as a contrast agent. EchoGen was administered as bolus IV injections. Activation was achieved by applying negative pressure (usually by suction in a syringe) which resulted in 2 micron sized microbubbles of gas in the circulation. The “activated” form of DDFPe has been shown to have more toxicity than "unactivated" compound (0.2 micron vesicles of DDFP without microbubbles). Recently, in a single- dose rat study, the maximum tolerated dose of "unactivated" DDFPe was determined to be 6 mL/kg, which converted to a human equivalent dose (HED) of approximately 1 mL/kg. At that dose in the rats, toxicity was observed to be impaired locomotion and blanching of the typical red color of the eyes and gums. No mortality was observed and all animals recovered within 4 hours.

Studies have also been performed in non-human primates. Anaesthetized rhesus monkeys received 0.6 mL/kg of activated DDFPe IV every 30 minutes for 3 doses without adverse effects[19]. In addition, conscious cynomolgus monkeys showed no adverse reactions to 0.6 mL/kg of activated DDFPe given IV every 30 minutes for 3 doses and showed only minor transient changes in blood pressure and heart rate at up to 1.1 mL/kg[19].

Additional information on the preclinical evaluation of DDFPe is presented in the Investigator's Brochure.

1.4 Clinical Trials

Pharmacokinetic data collected during studies conducted by Sonus were analyzed by NuvOx[16,17]. The pharmacokinetics of DDFP in human subjects exhibits biphasic decline after an IV bolus dose; there is a rapid initial decline followed by a slow terminal elimination phase[17]. The terminal elimination phase ($t_{1/2}$) in humans ranges from 81-99.5 min for doses of 0.15-0.35 mL/kg. The values of half-life in dogs (30-48 min) were shorter than humans. The half-life is the shortest in rats (0.7-1.9 min). Efficacy was demonstrated in lower levels in animal stroke models and higher levels are not thought necessary in humans.

DDFP is not metabolized in humans. The major route of excretion of DDFP is through expired air. Almost one hundred percent of administered dose was recovered in the expired air as DDFP. The clearance of DDFP in humans is 43.9-65.2 mL/min/kg.

1.5 Rationale for Conducting the Trial

A safe, reliable therapy deployed early in the care of acute stroke patients, either ischemic or hemorrhagic, that restored critical oxygen supply to brain could potentially attenuate ischemic tissue damage and could improve long-term patient outcomes. Immediate restoration of critical brain oxygenation to bridge the time to vascular reperfusion by other methods would be expected to decrease ischemic damage, improve immediate outcomes, decrease sequelae, and reduce long-term health care costs.

DDFPe (2% w/vol dodecafluoropentane emulsion (NVX-208)) is a liquid fluorocarbon, which transports over 200 times as much oxygen per milligram of fluorocarbon as liquid fluorocarbons that were previously tested extensively as oxygen therapeutics[13-15]. It can easily be injected intravenously. Intravenous drug delivery in the first hour after the onset of the symptoms and signs of stroke has been proven practical in the FAST MAG clinical trial of acute strokes[20].

We hypothesize that administration of DDFPe will provide critical tissue oxygenation in acute stroke patients to decrease stroke volumes and symptoms in these patients.

The rationale for administering the doses evaluated is:

1. The dose levels are within the levels already tested in animals and humans[6-11,16,17]. Volunteers received two IV bolus doses of 0.35 mL/kg of activated DDFPe 24 hours apart and brain cancer patients received daily doses of 0.17 mL/kg of unactivated DDFPe[19].

2. Therapeutic reversal of tumor hypoxia has already been observed in patients administered doses of 0.1 mL/kg and 0.17 mL/kg[19,21].

3. Therapeutic reduction in stroke damage has been observed at dose levels of 0.1 mL/kg in rabbits[6-11]. Since drug effects tend to correlate with body surface area/weight, one would predict that a dose of approximately 0.03 mL/kg should be effective in humans compared to rabbits. Therefore, we do not believe that it is necessary to explore doses higher than 0.17 mL/kg.

## 2.0 Objectives

### 2.1 Primary Objective

The primary objective of this study is to establish the Maximum Tolerated Dose (MTD) of DDFPe given intravenously at intervals of 90 ± 10 minutes x 3 doses within 12 hours after subjects have had a documented Acute Ischemic Stroke (AIS).

### 2.2 Secondary Objective

The secondary objective of this study is to assess the frequency and severity of adverse events following administration of DDFPe to patients who have had an AIS.

### 2.3 Exploratory Objective

We will evaluate the feasibility of using the National Institutes of Health Stroke Scale (NIHSS) to assess the immediate response to intravenous DDFPe in patients with AIS.

## 3.0 Study Design

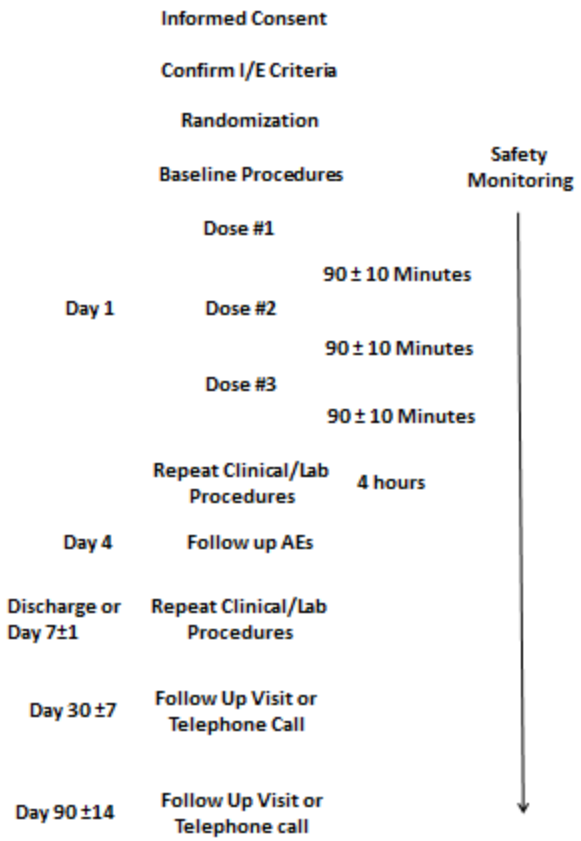
### 3.1 Study Design

This study is a randomized, placebo controlled, blinded escalating dose study designed to determine the MTD and adverse events possibly related to intravenous administration of DDFPe. At each of three dose levels (0.05, 0.10, 0.17 mL/kg) six subjects will receive DDFPe and two will receive placebo.

3.2 Study Schema

The study flow is shown below in Figure 1:

Figure 1: Study Schema




## 4.0 Trial Registration

The trial will be registered in the ClinicalTrials.gov database prior to enrollment of the first subject. Updated information will be included in the record every six (6) months or as necessary. Results will be included in the ClinicalTrials.gov database within one (1) year after the completion of the study.

## 5.0 Investigational Product

5.1 Description of the Investigational Product

DDFPe (2% w/vol dodecafluoropentane emulsion (NVX-208)) is a liquid fluorocarbon, which transports over 200 times as much oxygen per milligram of fluorocarbon as liquid fluorocarbons that were previously tested extensively as oxygen therapeutics. The active ingredient dodecafluoropentane (DDFP) is a liquid with a boiling point of 28-30°C at atmospheric pressure. It is formulated as a nanodroplet dispersion of 2% (w/v) DDFP, stabilized by a 0.3% (w/v) fluorosurfactant, PEG Telomer B, in a continuous phase of 30% (w/v) sucrose.

Clinical supplies for this study have been manufactured under aseptic conditions at NuvOx Pharma in Tucson, Arizona, USA. DDFPe is produced as a stable emulsion, which is terminally filtered through 0.2 μm sterile filters, and aseptically sealed in vials containing 10 mL of DDFPe.

The placebo will be a sterile 1:101 dilution of Intralipid® 20% IV fat emulsion in aqueous sodium chloride (0.9% w/v) for injection prepared by pharmacy staff according to instructions in the Pharmacy Manual. Immediately prior to injection, the placebo will be aseptically compounded and placed directly into the same dispensing syringes as those for dispensing used for the injection of DDFPe[22, 23]. The placebo will not be stored for any length of time.

5.2 Storage and Preparation of the Investigational Product

DDFPe will be shipped to the University of Arkansas for Medical Sciences (UAMS) Research Pharmacy prior to the start of the study along with instructions for handling, storage, dispensing and administration of DDFPe. All instructions are detailed in the Pharmacy Manual.

Receipt of drug in proper condition will be recorded by the research pharmacist. Upon receipt, any drug that does not meet the conditions established in the Pharmacy Manual or arrives with vials that are broken or otherwise damaged will be reported to NuvOx and instruction will be sought as to whether the vials can be used or should be set aside for later return or destruction. The site will be will be responsible for its own drug accountability.

DDFPe will be provided in 10 mL vials and stored upright at 2-8ºC at ambient humidity in a monitored refrigerator prior to use. Once a subject has been identified, the drug may be removed from the refrigerator and stored at room temperature up to 6 hours until administered. The study drug may not be frozen. All vials of DDFPe will be labelled for investigational use. The number of vials stored in each locked kit will be calculated to allow for administration of the maximum dose at each dosing level. Each kit will also have a table used to calculate the dose, drug dosing and accountability forms and will be labeled for investigational use only. Immediately prior to injection, DDFPe or placebo will be prepared as per instructions in the Pharmacy Manual by pharmacy staff. The syringes containing either DDFPe or placebo will be appropriately labeled for investigational use only and provided to the clinical team in a blinded manner.

Once a kit has been opened, it should be returned to the pharmacy after use.

## 5.3 Dose Escalation Plan

### 5.3.1 Dose Escalation

The plan for dose escalation is shown in Table 5.1.

**Table 5.1: Dose Escalation of DDFPe by Cohort**

| Cohort | DDFPe Dose (mL/kg) | Maximum Dose (mL) |
|---|---|---|
| 1 | 0.05 (x 3 doses) | 5 mL/dose x 3 doses |
| 2 | 0.10 (x 3 doses) | 10 mL/dose x 3 doses |
| 3 | 0.17 (x 3 doses) | 17 mL/dose x 3 doses |

* Subjects weighing more than 100kg will be included in the study. Doses will be limited to a maximum based on a weight of 100 kg for subjects weighing in excess of 100 kg.

### 5.3.2 Dose Limiting Toxicity

Dose limiting toxicity (DLT) will be defined by the following criteria:

- Clinically significant changes in vital signs:
  - Heart rate ± 50% from baseline
  - Respiratory rate >30 /min
  - Systolic blood pressure < 90 mmHg or >220 mmHg
  - Diastolic blood pressure >110 mmHg
- New (i.e. not seen at baseline) ECG changes consistent with:
  - Acute right ventricular dilation or strain
  - Incomplete or complete bundle branch block
  - Q waves in leads III and aVF
  - T-wave inversion and/or ST segment changes in the precordial leads
  - Any other clinically significant cardiac arrhythmia
- Common Terminology Criteria for Adverse Events (CTCAE) 4 Grade 3 or higher cough, dyspnea, chest pain-cardiac or non-cardiac, chest wall pain or hypoxia (See Appendix 1 for specific criteria)
- NIHSS: sudden worsening of 4 or more from the baseline (pre-DDFPe initiation)
- The Medical Monitor will review all data collected at Post-Dose #3 (approximately 4-6 hours after the end of the Dose #3 infusion of DDFPe or placebo for each subject). Enrollment will be on hold until the Medical Monitor has reviewed the data and approves enrollment of an additional subject. The Medical Monitor may choose to temporarily halt the study if serious concerns arise regarding subject safety.

### 5.3.3 Maximum Tolerated Dose

The algorithm for determining the MTD is as follows:

- Up to six subjects and two controls will be enrolled at each dose level constituting each cohort. Subjects will be evaluated for four hours after receiving the last of the three doses and again at discharge from the hospital or one week later, whichever is sooner.
- DLT is previously defined in Section 5.3.2.
- If no DLTs are observed in a patient at Post-Dose #3 of DDFPe or placebo the Medical Monitor may allow progression to the next patient.

- After all 8 subjects have been enrolled in a cohort, the Medical Monitor will review the data. A decision as to whether the study may proceed to the next cohort will be made.
- If a total of two or fewer subjects in an 8 subject cohort experience a DLT, escalation to the next cohort may proceed if approved by the Medical Monitor. If three or more DLTs were observed, the Medical Monitor may consult with the Research Pharmacist to determine if the observed DLTs occurred in subjects who received DDFPe or placebo. If any of the DLTs were observed in the subjects receiving placebo, the Medical Monitor may allow the study to proceed as long as two or fewer subjects with DLTs received DDFPe.
- If three or more subjects who received DDFPe in an 8 subject cohort experience a DLT, the MTD will be determined to have been exceeded and further enrollment in the cohort as well as dose escalation will stop. The dose administered to the previous cohort will be considered to be the MTD.
- Subjects who withdraw from the study for reasons other than a DLT may be replaced.
- The Medical Monitor will review all safety data for each patient and cohort and must grant approval before proceeding to the next patient and/or cohort.
- Exploration of lower dose levels intermediate to a level previously shown to be well tolerated may be considered. In addition to reducing the dose, this might include reducing the number of doses, increasing the time between doses, and/or altering the infusion time.
- The dose exploration will be complete when either: (1) the MTD has been defined or (2) when no MTD has been reached but six subjects and two controls have been treated at the last cohort level approved by the Medical Monitor.

5.4 Dispensing of the Investigational Product

DDFPe will be stored as detailed in Section 5.2. A written order signed by one of the principal investigators must be obtained prior to dispensing.

5.5 Administration of the Investigational Product

For each cohort, the dose of DDFPe or placebo will be calculated based on body weight according to the table in Appendix 2. Before administration, the drug will be prepared for injection per instructions in the Pharmacy Manual. DDFPe will be administered intravenously over 5-10 minutes through an IV catheter placed in a peripheral vein or through a central venous catheter (Note: a central venous catheter will not be placed solely for the study). The site of the intravenous catheter through which the study drug is administered will be recorded in the research record. Doses will be administered by slow IV push. After the first dose, subsequent doses will be administered 90 ± 10 minutes after the end of the previous infusion. Administration of all doses should occur with the syringe in the vertical position assuring that any

product foaming in the syringe will float near the rubber seal of the syringe plunger (NOTE: THIS IS THE MOST CRITICAL SAFETY CONSIDERATION DURING INFUSION). The placebo will be placed in identical syringes and administered in the same way. The volume of drug product to be used from each syringe will be provided on the label from pharmacy. The start and stop times for each infusion will be recorded on the source documents. The volume of the infusion will also be recorded.

5.6 Prior and Concomitant Therapy

5.6.1 Excluded Drug Therapy Prior to Enrollment

Blood clot lysing agents normally used in patients with non-hemorrhagic stroke may be used as indicated for acute treatment of AIS. Acute or chronic dosing with the following medications precludes entry into the study:

- Anticoagulants with the exception of low dose aspirin, prophylactic doses of low molecular weight heparin and warfarin
- All non-prescription medications and herbal remedies must be reviewed and approved by the investigator.
- NSAIDs are permissible.

5.6.2 Prohibited Drug Therapy During and 24 Hours after the Administration of the Investigational Product

The following drugs are not allowable within 24 hours after the last dose of DDFPe:

- None

5.6.3 Criteria for Stopping the Investigational Product

The investigational agent will be discontinued in the event that:

- Life-threatening disease progression occurs
- Unacceptable adverse events
- Subject wishes to withdraw from the study
- Changes in the patient's condition that, in the opinion of the investigator, present unacceptable risk to the subject

5.7 Return and Destruction of the Investigational Product

Any doses of DDFPe or placebo that are dispensed but not administered to an individual subject will be returned to the Pharmacy, documented in the drug accountability record, and handled as per Section 5.5. Any DDFPe or placebo that remains at the end of the study will be entered into the drug accountability records and returned to NuvOx or destroyed (21 CFR 312.62). Destruction will be witnessed and recorded appropriately.

## 6.0 Study Subjects

6.1 Study Population

The study population will include any male or female patients, ages 18years old or older, who present to UAMS with evidence of an AIS. The potential subjects must have a CT scan demonstrating that there is no evidence of hemorrhage or major

trauma. Potential subjects must not have had recent (within 3 months) intracranial surgery. Subjects must meet all of the inclusion and exclusion criteria prior to enrollment. The patient or a legally authorized representative must be able and willing to provide informed consent.

6.2 Inclusion Criteria

6.2.1 Ages 18 years old or older
6.2.2 Diagnosis of AIS
6.2.3 Body weight ≥ 45 kg
6.2.4 NIHSS between 2 and 20 inclusive.
6.2.5 Patient or LAR must be willing and able to understand the study and provide written informed consent

6.3 Exclusion Criteria

6.3.1 Currently pregnant or breastfeeding
6.3.2 History of significantly impaired renal or hepatic function
6.3.3 Severe hemorrhage or severe hemorrhagic stroke on CT scan. Mild or moderate changes of Fisher Grade 1 or 2 subarachnoid hemorrhage are allowed as are hemorrhagic transformation changes of Grade HI-1 and HI-2[24,25].
6.3.4 Prior stroke, intracranial surgery, or major head trauma within three (3) months prior to enrollment
6.3.5 Pre-stroke mRS ≥ 2 (See Appendix 3)
6.3.6 Myocardial infarction within six (6) months prior to enrollment
6.3.7 Unstable angina, NYHA Class II or greater congestive heart failure
6.3.8 Uncontrolled hypertension (SBP > 180 and/or DBP > 110 mmHg)
6.3.9 Uncontrolled arrhythmia or history of clinically significant arrhythmia within the past six (6) months (except atrial fibrillation)
6.3.10 Clinically significant COPD or other pulmonary condition that is not controlled by medication or requires oxygen frequently or continuously
6.3.11 Pneumonia, bronchitis, or other acute respiratory disease
6.3.12 Current anticoagulant therapy except for antiplatelet therapy (aspirin, NSAIDs) and prophylactic doses of low molecular weight heparin to prevent deep vein thrombosis. Note: tPA administered as part of subjects' therapy for AIS is allowed. However, thrombolytic therapy is not a study requirement.
6.3.13 History of allergic reaction attributed to compounds of similar chemical composition to DDFPe or soy or egg allergies (see Investigator's Brochure).
6.3.14 Subject has received any investigational drug within thirty (30) days prior to enrollment into the study
6.3.15 Inability to comply with the study procedures
6.3.16 History or evidence of any other clinically significant condition that, in the opinion of the investigator, might pose a safety risk to subjects or interfere with study procedures, evaluation, or completion

6.4 Withdrawal Criteria

Subjects may choose to withdraw from the study at any time for any reason. Additionally, the investigator may choose to remove subjects from the study. Any subject withdrawing their consent to participate in the study or their authorization to use their protected health information will be withdrawn from the study.

Subjects will be informed that the investigational product may be discontinued by the investigator even if the subject and/or the LAR wish to continue. This may occur for the following reasons:

- Serious Adverse Event (SAE) believed to be related to investigational product
- Intolerable side effects
- Failure to complete required study procedures
- Clinically significant laboratory or ECG abnormalities
- Significant change in oxygenation as measured by pulse oximetry
- Initiation of treatment with a prohibited drug during the intervention phase
- Non-compliance with the treatment regimen

Subjects may also be withdrawn for any reason if the investigator believes that it is in the best interest of the subject to discontinue the study.

6.5 Replacement of Subjects

Subjects who withdraw or are withdrawn from the study prior to the completion of the Day 7 visit may be replaced at the discretion of the investigator.

## 7.0 Investigational Plan

7.1 Usual Care Provided by Treating Physician

Customary (routine) care for patients suffering a stroke will be offered as would be the case had the patient not enrolled in the trial. This may include physiological monitoring, medical procedures, drug therapy (including tPA), respiratory support, and ancillary or accessory care. Routine care will be directed by the patient's treating physician. If the treating physician believes that it is no longer in the best interest for the patient to continue in the study, he/she will contact the investigator and immediately stop all study-related procedures.

7.2 Consent Process

Potential study subjects whose condition has rendered them unable to provide informed consent due to aphasia, confusion, impaired consciousness or other cognitive impairments such as intellectual disability and dementia will require a legally authorized representative (LAR).

Trained study personnel will review the IRB-approved study summary brochure with the subject/LAR and answer questions followed by reviewing the informed consent document with the subject and/or a LAR. The subject/LAR will be allowed to ask questions. If the subject/LAR agrees to participate, the consent will be signed and a copy will be provided to the subject. Once the consent process is complete, study

personnel will document the process in a note to be placed in the study file along with the signed consent document.

All screened and enrolled subjects will be recorded in the Screening and Enrollment Log at each participating institution. All enrolled subjects should be reported to Dr. Culp within 24 hours using the Study Participant Registration form. Dr. Culp will advise all PIs as to when it is acceptable to proceed with the next subject. All pre-determined stopping points will be observed (i.e. after each subject in each cohort and at the end of each cohort prior to proceeding to the next highest dose).

7.3 Verification of Inclusion/Exclusion Criteria

After the consent process is complete, trained study personnel will review the Inclusion and Exclusion criteria with the subject/LAR. The following options are then possible:

- If the subject meets all criteria, they will be allowed to proceed with the study.
- If the subject fails to meet criteria, no further study-related procedures will be conducted.
- If the failure to meet criteria is minor, the investigator may choose to approach the Medical Monitor for a waiver. A waiver will be granted only if doing so will not place the subject at increased risk if allowed to participate in the study.

Study personnel will document the review of Inclusion and Exclusion Criteria on the appropriate form and place the signed form in the study file. The investigator will be notified of the results of the review.

7.4 Randomization and Blinding

7.4.1 A randomization schedule will be created and maintained by the UAMS Research Pharmacy.

7.4.2 Subjects who agree to participate in the study and meet inclusion and exclusion criteria will be assigned to the next available treatment. The UAMS Research Pharmacy will track enrollment and randomize blinded treatments for administration to properly enrolled research subjects.

7.4.3 The UAMS Research Pharmacy will deliver the blinded investigational treatment to the study personnel who will administer the drug to the subject.

7.5 Screening Study Procedures

7.5.1 Screening and Enrollment Log

All subjects who provide informed consent will be entered into the screening and enrollment log. Once screening is complete, the log will be updated to identify those subjects who pass screening and proceed into the dosing phase of the trial.

7.5.2 Review of Head CT Exam

The investigator will review the CT of the head with the treating physician (if not the investigator) or radiologist to assure that the subject meets the

eligibility criteria. The CT must be negative for severe hemorrhage or sever hemorrhagic stroke. This will be documented in the study record.

7.5.3 Medical History

A brief medical history reviewing information pertinent to the study will be completed by the investigator. The medical history will be documented and signed by the investigator (physician).

7.5.4 Physical Exam

A brief, targeted physical exam will be completed by the investigator to document the subjects condition and assure that there are no obvious reasons that it would not be in the best interest of the subject to proceed with the study. Weight will be measured in light clothing without shoes and recorded in the study record. Physical findings will be documented and signed by the investigator (physician).

7.5.5 Concomitant Medications

All medications currently taken by subjects will be reviewed and documented on the appropriate form. The form will be included in the study file.

7.5.6 Pregnancy Test

A serum pregnancy test will be performed on all women of child-bearing potential. Dosing with DDFPe will not begin before the test confirms that the women are not pregnant. If the test indicates that a woman is pregnant, she will be immediately dropped from the study.

7.5.7 NIH Stroke Scale

The NIHSS will be administered during Screening to assure that subjects score between 2 and 20, inclusive, to meet the study Inclusion criteria. Initial NIHSS scores from outside originating hospitals or facilities are acceptable only if performed by a certified neurologist. The NIHSS will be repeated throughout the study as indicated in the Schedule of Time and Events (Appendix 4). The NIHSS may be found at:
https://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf

7.5.8 ECG

A 12-lead ECG will be performed as part of the Screening process to assure that subjects with serious arrhythmias are appropriately excluded from the study. The ECG will be inspected by the treating physician and the investigator. If a serious rhythm disturbance is observed, a cardiologist may be consulted to confirm the findings. If confirmed by the cardiologist, the subject will be withdrawn from the study prior to administration of DDFPe. After the study is completed, all ECGs will be reviewed by a board certified cardiologist to confirm that no new arrhythmias developed during the course of treatment.

7.5.9 Laboratory Studies

All subjects will have the following laboratory tests collected prior to receiving DDFPe:

- Complete Blood Count
- Electrolytes (Na, K, Cl,)
- BUN
- Creatinine
- LFTs (AST, ALT, Total Bilirubin, Direct Bilirubin, Albumin)
- Calcium
- Glucose

It is anticipated that many of these tests will be done as part of the subjects' routine care. These tests will provide baseline values prior to administration of DDFPe for later comparison with post-dosing test results. The results of these tests may or may not be available prior to dosing with DDFPe. None of the tests would exclude a subject from participating in the study.

7.6 Day 1: Study Procedures

After documentation that the subject passed the screening procedures and meets all Inclusion and Exclusion criteria, study personnel will check to assure that a patent intravenous catheter is in place for infusion of the DDFPe. The catheter should be used solely for infusion of DDFPe and compatible intravenous fluids during the study intervention period (from the initiation of Dose #1 to after the Dose #3 infusion is complete).

**Dose #1:** DDFPe will be ordered from the pharmacy and prepared as previously described. The time that the infusion begins will be recorded. The drug or placebo will be infused over 5-10 minutes. At the end of the infusion, the time will again be recorded. Vital signs and pulse oximetry will be monitored. Measurements will be recorded every 15 minutes. The subject will be observed for any signs of adverse events for 90 minutes after the completion of the infusion.

**Dose # 2:** Any new concomitant medications will be recorded. The second dose of DDFPe or placebo will be administered as previously described over 5-10 minutes. Times will be recorded at the beginning and end of the infusion as before. Vital signs and pulse oximetry will be monitored. Measurements will be recorded every 15 minutes. The NIHSS will be repeated within 60 minutes after the end of the DDFPe infusion. The subject will be observed for any signs of adverse events for 90 minutes after the completion of the infusion.

**Dose #3:** Any new concomitant medications will be recorded. The third dose of DDFPe or placebo will be administered as previously described over 5-10 minutes. Times will be recorded at the beginning and end of the infusion as before. Vital signs and pulse oximetry will be monitored. Measurements will be recorded every 15 minutes. The NIHSS will be repeated within 60 minutes after the end of the DDFPe

infusion. The subject will be observed for any signs of adverse events for 90 minutes after the completion of the infusion.

Vitals should be taken at all scheduled time points (i.e. every 15 minutes); however, deviations from scheduled times will not be considered protocol deviations. The exact date and time of each measurement will be recorded on the CRF.

**Post-Dose #3:** Approximately 4±1 hours after the end of Dose #3, the following observations will be made:

- Concomitant medications administered after Dose #3
- A brief physical examination
- Vital signs (BP, HR, RR)
- Pulse oximeter measurement
- NIHSS
- ECG
- Laboratory testing

Any AEs observed during the intervention period will be recorded, assessed, and followed to resolution.

7.7 Day 4: Study Procedures

All subjects will be contacted to assess AEs. If the subject is still hospitalized, any significant change in condition will be recorded as a possible AE and assessed by the investigator. All AEs will be graded (mild, moderate, severe), assessed for relatedness (not related, possibly related, probably related, definitely related), and followed to resolution as described in Section 8.0.

In the event that the subject has been discharged from the hospital before Day 4, subjects or their LAR will be contacted by telephone. AEs will be assessed and followed as described above.

7.8 Day 7±1 (or Hospital Discharge Day): Study Procedures

The subject will be re-examined on the day of discharge or at one week (Day 7±1), whichever comes first. At this visit, the following procedures will be completed:

- A brief interval medical history
- A brief physical examination
- Vital signs (BP, HR, RR)
- Pulse oximeter measurement
- NIHSS
- ECG
- Laboratory testing
- Modified Rankin Scale

Any AEs observed during the intervention period will be recorded, assessed, and followed to resolution.

If subjects are discharged before Day 7, they will be contacted by telephone to assess possible AEs seven days after administration of the investigational product. If any possible AEs are identified, they will be assessed and followed as previously described.

7.9 Day 30 (±7 days): Study Procedures or Telephone Follow Up

This visit will occur as part of the routine, clinically indicated follow up. If no routine appointment is scheduled, the subject may be contacted by telephone to complete the study visit. At this visit, the following procedures will occur:

- Interval medical history
- A brief physical examination (omitted for telephone follow up)
- Vital signs (BP, HR, RR) (omitted for telephone follow up)
- mRS
- NIHSS (omitted for telephone follow up)
- Adverse Events

7.10 Day 90 (±14 days): Office Visit or Telephone Follow Up

This visit will occur as part of the routine, clinically indicated follow up. If no routine appointment is scheduled, the subject may be contacted by telephone to complete the study visit. The purpose of this visit is to assess longer term complications and functioning related to stroke. At this visit, the following procedures will occur:

- Interval medical history
- mRS
- Adverse Events

The medical history will focus on additional cardiovascular events that may have occurred since the stroke, any changes in functioning at 90 days compared with pre-stroke.

## 8.0 Adverse Events

8.1 Definitions

**Adverse Event**

An adverse event (AE) is any untoward medical occurrence that develops or worsens in severity during the course of the study, whether or not it has a causal relationship to the study treatment. Concurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered AEs if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

**Serious Adverse Event**

Adverse events are classified as serious or non-serious. A ***serious adverse event (SAE)*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

**Adverse Event Reporting Period**

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as within 90 days following the last administration of study treatment.

**Preexisting Condition**

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period (e.g. if behavior worsens).

**General Physical Examination Findings**

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an AE.

**Post-study Adverse Event**

All unresolved AEs should be followed by the investigator until the events are resolved, until the events are otherwise stable or the subject is lost to follow-up. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

**Abnormal Laboratory Values**

A clinical laboratory abnormality should be documented as an AE if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the investigational product, more frequent follow-up assessments, further diagnostic investigation, etc.

**Hospitalization, Prolonged Hospitalization or Surgery**

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

## 8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document and grouped under one diagnosis when possible.

All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome.

## 8.3 Reporting Procedures for Adverse and Serious Adverse Events

All adverse and SAEs will be reported in accordance with FDA and local IRB requirements. In addition, any SAE will be reported to NuvOx and the Sponsor by the Investigator within 24 hours after becoming apparent.

All SAEs that meet the IRB's UPIRTSO requirements must be submitted to the IRB within 10 working days. All other SAEs will be submitted to the IRB at continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

### 8.4 Data Safety and Monitoring Plan

All safety data will be reviewed by the Medical Monitor after each patient and after the completion of each cohort. All moderate and severe safety signals that are unanticipated and probably or definitely related to the investigational product will be discussed with the Sponsor and NuVox prior to enrolling additional subjects. A Data Safety and Monitoring Board will not be appointed.

### 8.5 Medical Monitor

A Medical Monitor (MM) will be selected. The MM will be a licensed physician who is familiar with cardiovascular disease and stroke. The MM will review the data collected after each patient and after each dose level and will provide an opinion to the investigator as to whether it is advisable to proceed with dose escalation as described in Section 5.3.3. As part of the review, the MM will review all AEs and assure that any SAEs have been reported appropriately.

### 8.6 Risks and Benefits

Risks may include pain from IV placement, hypotension, reversible inflammatory changes in the lungs, nausea, vomiting, drowsiness, dizziness, fever, headache, reduced or elevated blood pressure, blanching of the gums, and allergy to soy or eggs. There may be unanticipated adverse events or outcomes. It is anticipated that oxygen delivery to ischemic areas of the brain may improve thereby changing clinical signs. It is unclear as to whether this might result in reduced cerebral tissue loss or any improvement in outcome following stroke. There may be no benefit to subjects.

### 8.7 Risk Mitigation

All subjects will be observed in a unit accustomed to treating patients with stroke. Customary clinical care will be provided by the patient's treating physician. No standard treatments will be withheld as a result of participation in the study.

Adverse events will be actively sought through the study at multiple time points. All AEs will be recorded and evaluated for severity and relatedness and followed to resolution. A MM will be appointed to review safety issues as described in Section 8.5. Repeated measurement of clinical, ECG, and laboratory data have been included to detect important safety signals. Careful assessment of all AEs, especially those that are probably or definitely related to the investigational product, will be conducted.

## 9.0 Data Collection

### 9.1 Data Collection and Storage

All source data will be recorded on Case Report Forms (CRFs) as described in Sections 9.4 and 9.5. CRFs will be placed in the subjects' study file and stored in a

locked file cabinet or on password protected or encrypted electronic media. All data will be appropriately monitored by the sponsor to assure data quality and integrity. Electronic data capture will not be used in this study.

9.2 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Information Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- The personal health information (PHI) to be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- To whom the data may be disclosed and the reasons for this disclosure
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.3 Study Monitoring and Data Queries

The investigator is required to permit the Sponsor to monitor the study data, including all communications with the IRB, the manufacturer, all source documents, CRFs, pharmacy records, and any other pertinent information. Monitoring visits will be scheduled at a time that is convenient for both the monitor and the investigator. The monitor will provide a written report to the investigator within one month after the conclusion of the monitoring visit.

9.4 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.5 Case Report Forms

The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a

space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

### 9.6 Study Auditing

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the study Sponsor, government regulatory bodies, and UAMS compliance groups of all study related documents (e.g. source documents, regulatory documents, pharmacy documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices. FDA may choose to inspect the study records as indicated in 21 CFR 312.58.

### 9.7 Record Retention

It is the investigator's responsibility to retain study essential documents for 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated (21 CFR 312.62). These documents should be retained for a longer period if required by an agreement with the funding entity or the supplier of the investigational agent. In such an instance, it is the responsibility of the funding entity or supplier of the investigational product to inform the investigator/institution as to when these documents no longer need to be retained.

## 10.0 Data Analysis Plan

### 10.1 Sample Size

This is a Phase I study. No sample size estimates were done.

### 10.2 Clinical Data

Demographic data will be presented as the mean ± SD (range) for normally distributed data (median ± interquartile range for non-normal data).

Clinical data includes vital signs and pulse oximetry (pre- and post-intervention). Pre- and post-intervention data will be grouped and examined for differences using a two-sided t-test or ANOVA, as appropriate. Pre- and post- laboratory data will be compared in a similar manner. ECGs will be read by a board-certified cardiologist and clinically significant changes will be described.

10.3 Safety Data

All safety data will be reported. DLT will be examined and the MTD will be determined as previously described. All SAEs will be reported as required.

10.4 Exploratory Aim Analysis

There are a number of patient subgroups that could be of interest and might be expected to respond differently to DDFPe as evaluated by NIHSS scores:

a. In those early patients who get some successful therapy and get DDFPe early at less than 3 hours from LKWT, the values should drop with the DDFPe and stay down with reperfusion. Late DDFPe uncertain.
b. In those that get Rx and it fails, scores may perhaps go down with early DDFPe and come back up when it wears off. With late DDFPe little change is expected.
c. In those that do not get reperfusion therapy and do get DDFPe in the first 3 hours, scores should go down but come back up when it wears off.
d. In those that do not get reperfusion therapy and get DDFPe late, scores should not change much
e. In those that get placebo, should see little change, early or late, unless they have successful reperfusion therapy or spontaneous reperfusion.

Fewer than 20% are likely to get IV tPA or IA reperfusion therapy of the total 24 patients; the patient numbers in any of these groups will be quite small, obviating the ability to make formal statistical comparisons or to draw conclusions about the impact of DDFPe therapy on outcome. This is a Phase I safety trial, and not designed to test treatment outcomes. As an exploratory analysis, we will compare the patients without reperfusion therapy, IV or IA, who got early DDFPe under 3 hours from LKWT, to placebo patients of similar characteristics. Due to the small sample sizes and because each of the proposed doses were effective in animal studies, we will ignore dose in this comparison.

We expect that the NIHSS values should drop with DDFPe but come back up after 5 or 6 hours and no change is expected in placebo. We will visually examine plots of the data for consistency with this hypothesis and if the sample sizes are sufficient, we will carry out nonparametric tests comparing the changes as exploratory analyses.

Those patients receiving DDFPe between 3 and 6 hours from LKWT could be another group of great interest, and we will make similar exploratory comparisons of this group with the two just described.

No claims of efficacy will be possible based on these limited data, but they may suggest directions for subsequent study.

## 11.0 Ethical and Regulatory Requirements

11.1 Trial Registration

The trial will be registered on ClinicalTrials.gov as previously described in Section 4 of the protocol.

11.2 Informed Consent Procedures

This study will be conducted in accordance with all applicable government regulations, research policies and procedures. This protocol and any amendments will be submitted and approved by the local IRB prior to conducting the study.

The formal consent of each subject/LAR, using the IRB-approved consent form, will be obtained before the subject is enrolled into any study procedure. All subjects/LARs for this study will be provided a consent form describing this study and provided sufficient information in language suitable for subjects/LARs to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. It is anticipated that, due to the nature of the condition under study, some subjects may be unable to provide informed consent. The investigators will follow local IRB policies for obtaining consent from cognitively impaired subjects.

No coercion or undue influence will be used in the consent process. The consent form must be signed by the subject/LAR and the individual obtaining the consent. A copy of the signed consent will be given to the subjects/LARs, and the informed consent process will be documented in each subject's research record.

11.3 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

This study is to be conducted according to applicable government regulations and Institutional research policies and procedures. The protocol, the consent document, and any amendments will be submitted to a properly constituted independent IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the local IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

11.4 Subject Confidentiality

Every effort will be made to assure that data collected from subjects remains confidential. Subjects will be identified by a code. The subject's name and identifying information will be stored in a locked file in the office of the investigator or on a password protected or an encrypted drive in the investigators' personal possession. Data may be shared with NuvOx, the Sponsor (UAMS), the IRB, the FDA, and appropriate compliance and regulatory authorities.

11.5 Protocol Amendments

Any change to the research protocol or consent document must be submitted to and receive approval from the Sponsor, NuVox, and the IRB prior to implementation.

11.6 Study Termination

The study may be terminated at any time by the Sponsor or NuvOx. If the study is terminated, the FDA will be notified.

In the event that the study is terminated prior to completion, all investigational product will be returned to the pharmacy. The pharmacy will either return the unused product to NuvOx or proceed with destruction of the investigational agent per 21 CFR 312.62.

## 12.0 Publication Policy

Any manuscripts reporting the results of this clinical trial must be provided to NuvOx by the Principal Investigator for advisory review and comment prior to submission for publication. NuvOx will have 30 days from the date of receipt for review and will also have the right to request that publication be delayed for up to an additional 30 days in order to ensure that confidential and proprietary data, and intellectual property rights, are protected. Copies of meeting abstracts must be provided to NuvOx for courtesy review as soon as possible and at least three (3) days prior to submission. Press releases and other media presentations must also be forwarded to NuvOx prior to release.

In any publication or presentation, individual subjects will not be identified by name or any other means. All data will be published in aggregate form.

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## Appendices:

Appendices 1 – 4 are attached below.

## Appendix 1: CTCAE 4 Selected Adverse Events

| **Respiratory, thoracic, and mediastinal disorders** | | | | | |
|---|---|---|---|---|---|
| | **Grade** | | | | |
| **Adverse Event** | **1** | **2** | **3** | **4** | **5** |
| Cough<br>Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound. | Mild symptoms; nonprescription intervention indicated | Moderate symptoms, medical intervention indicated; limiting instrumental ADL | Severe symptoms; limiting self care ADL | | |
| Dyspnea<br>Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing. | Shortness of breath with moderate exertion | Shortness of breath with minimal exertion; limiting instrumental ADL | Shortness of breath at rest; limiting self care ADL | Life-threatening consequences; urgent intervention indicated | Death |
| Chest Pain Cardiac<br>Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation. | Mild pain | Moderate pain; limiting instrumental ADL | Pain at rest; limiting self care ADL | | |
| Chest Wall Pain<br>Definition: A disorder characterized by marked discomfort sensation in the pleura. | Mild pain | Moderate pain; limiting instrumental ADL | Severe pain; limiting self care ADL | | |
| Hypoxia<br>Definition: A disorder characterized by a decrease in the level of oxygen in the body. | | Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen | Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg | Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation) | Death |

## Appendix 2: DDFPe Dosing by Weight

DDFPe dosage volume in cc for **0.05 mL/kg** based on patient body weight in kilograms (kg).

| Body Weight (kg) | DDFPe Dose 0.05mL/ kg (mL) | Number of DDFPe 10mL Vials Required | Number of 10mL Syringes | Total Volume to be Prepared (mL) | Volume to be Administered from syringe (mL) |
|---|---|---|---|---|---|
| 45* | 2.2 | 1 | 1 | 10 | 2.2 |
| 46 | 2.3 | 1 | 1 | 10 | 2.3 |
| 47 | 2.4 | 1 | 1 | 10 | 2.4 |
| 48 | 2.4 | 1 | 1 | 10 | 2.4 |
| 49 | 2.4 | 1 | 1 | 10 | 2.4 |
| 50 | 2.5 | 1 | 1 | 10 | 2.5 |
| 51 | 2.6 | 1 | 1 | 10 | 2.6 |
| 52 | 2.6 | 1 | 1 | 10 | 2.6 |
| 53 | 2.6 | 1 | 1 | 10 | 2.6 |
| 54 | 2.7 | 1 | 1 | 10 | 2.7 |
| 55 | 2.8 | 1 | 1 | 10 | 2.8 |
| 56 | 2.8 | 1 | 1 | 10 | 2.8 |
| 57 | 2.8 | 1 | 1 | 10 | 2.8 |
| 58 | 2.9 | 1 | 1 | 10 | 2.9 |
| 59 | 3.0 | 1 | 1 | 10 | 3.0 |
| 60 | 3.0 | 1 | 1 | 10 | 3.0 |
| 61 | 3.0 | 1 | 1 | 10 | 3.0 |
| 62 | 3.1 | 1 | 1 | 10 | 3.1 |
| 63 | 3.2 | 1 | 1 | 10 | 3.2 |
| 64 | 3.2 | 1 | 1 | 10 | 3.2 |
| 65 | 3.2 | 1 | 1 | 10 | 3.2 |
| 66 | 3.3 | 1 | 1 | 10 | 3.3 |
| 67 | 3.4 | 1 | 1 | 10 | 3.4 |
| 68 | 3.4 | 1 | 1 | 10 | 3.4 |
| 69 | 3.4 | 1 | 1 | 10 | 3.4 |
| 70 | 3.5 | 1 | 1 | 10 | 3.5 |
| 71 | 3.6 | 1 | 1 | 10 | 3.6 |
| 72 | 3.6 | 1 | 1 | 10 | 3.6 |
| 73 | 3.6 | 1 | 1 | 10 | 3.6 |
| 74 | 3.7 | 1 | 1 | 10 | 3.7 |
| 75 | 3.8 | 1 | 1 | 10 | 3.8 |
| 76 | 3.8 | 1 | 1 | 10 | 3.8 |
| 77 | 3.8 | 1 | 1 | 10 | 3.8 |
| 78 | 3.9 | 1 | 1 | 10 | 3.9 |
| 79 | 4.0 | 1 | 1 | 10 | 4.0 |
| 80 | 4.0 | 1 | 1 | 10 | 4.0 |

| Body Weight (kg) | DDFPe Dose 0.05mL/ kg (mL) | Number of DDFPe 10mL Vials Required | Number of 10 mL Syringes | Total Volume to be Prepared (mL) | Volume to be Administered from syringe (mL) |
|---|---|---|---|---|---|
| 81 | 4.0 | 1 | 1 | 10 | 4.0 |
| 82 | 4.1 | 1 | 1 | 10 | 4.1 |
| 83 | 4.2 | 1 | 1 | 10 | 4.2 |
| 84 | 4.2 | 1 | 1 | 10 | 4.2 |
| 85 | 4.2 | 1 | 1 | 10 | 4.2 |
| 86 | 4.3 | 1 | 1 | 10 | 4.3 |
| 87 | 4.4 | 1 | 1 | 10 | 4.4 |
| 88 | 4.4 | 1 | 1 | 10 | 4.4 |
| 89 | 4.4 | 1 | 1 | 10 | 4.4 |
| 90 | 4.5 | 1 | 1 | 10 | 4.5 |
| 91 | 4.6 | 1 | 1 | 10 | 4.6 |
| 92 | 4.6 | 1 | 1 | 10 | 4.6 |
| 93 | 4.6 | 1 | 1 | 10 | 4.6 |
| 94 | 4.7 | 1 | 1 | 10 | 4.7 |
| 95 | 4.8 | 1 | 1 | 10 | 4.8 |
| 96 | 4.8 | 1 | 1 | 10 | 4.8 |
| 97 | 4.8 | 1 | 1 | 10 | 4.8 |
| 98 | 4.9 | 1 | 1 | 10 | 4.9 |
| 99 | 5.0 | 1 | 1 | 10 | 5.0 |
| 100** | 5.0 | 1 | 1 | 10 | 5.0 |

Total DDFPe Dose = 0.05 mL/kg x weight in kg.
*Minimum subject weight = 45 kg.
**Maximum subject weight used for dose calculation = 100 kg. For subjects weighing more than 100 kg, dose will be calculated based on a weight of 100 kg.

DDFPe dosage volume in cc for **0.10 mL/kg** based on patient body weight in kilograms (kg).

| Body Weight (kg) | DDFPe Dose 0.10mL/kg | Number of DDFPe 10mL Vials Required | Number of 10mL Syringes to be Prepared | Total Volume to be Prepared (mL) | Volume to be Administered from 1st syringe (mL) | Volume to be Administered from 2nd Syringe (mL) |
|---|---|---|---|---|---|---|
| 45* | 4.5 | 1 | 1 | 10 | 4.5 | N/A |
| 46 | 4.6 | 1 | 1 | 10 | 4.6 | N/A |
| 47 | 4.7 | 1 | 1 | 10 | 4.7 | N/A |
| 48 | 4.8 | 1 | 1 | 10 | 4.8 | N/A |
| 49 | 4.9 | 1 | 1 | 10 | 4.9 | N/A |
| 50 | 5.0 | 1 | 1 | 10 | 5.0 | N/A |
| 51 | 5.1 | 1 | 1 | 10 | 5.1 | N/A |
| 52 | 5.2 | 1 | 1 | 10 | 5.2 | N/A |
| 53 | 5.3 | 1 | 1 | 10 | 5.3 | N/A |
| 54 | 5.4 | 1 | 1 | 10 | 5.4 | N/A |
| 55 | 5.5 | 1 | 1 | 10 | 5.5 | N/A |
| 56 | 5.6 | 1 | 1 | 10 | 5.6 | N/A |
| 57 | 5.7 | 1 | 1 | 10 | 5.7 | N/A |
| 58 | 5.8 | 1 | 1 | 10 | 5.8 | N/A |
| 59 | 5.9 | 1 | 1 | 10 | 5.9 | N/A |
| 60 | 6.0 | 1 | 1 | 10 | 6.0 | N/A |
| 61 | 6.1 | 1 | 1 | 10 | 6.1 | N/A |
| 62 | 6.2 | 1 | 1 | 10 | 6.2 | N/A |
| 63 | 6.3 | 1 | 1 | 10 | 6.3 | N/A |
| 64 | 6.4 | 1 | 1 | 10 | 6.4 | N/A |
| 65 | 6.5 | 1 | 1 | 10 | 6.5 | N/A |
| 66 | 6.6 | 1 | 1 | 10 | 6.6 | N/A |
| 67 | 6.7 | 1 | 1 | 10 | 6.7 | N/A |
| 68 | 6.8 | 1 | 1 | 10 | 6.8 | N/A |
| 69 | 6.9 | 1 | 1 | 10 | 6.9 | N/A |
| 70 | 7.0 | 1 | 1 | 10 | 7.0 | N/A |
| 71 | 7.1 | 1 | 1 | 10 | 7.1 | N/A |
| 72 | 7.2 | 1 | 1 | 10 | 7.2 | N/A |
| 73 | 7.3 | 1 | 1 | 10 | 7.3 | N/A |
| 74 | 7.4 | 1 | 1 | 10 | 7.4 | N/A |
| 75 | 7.5 | 1 | 1 | 10 | 7.5 | N/A |
| 76 | 7.6 | 1 | 1 | 10 | 7.6 | N/A |
| 77 | 7.7 | 1 | 1 | 10 | 7.7 | N/A |
| 78 | 7.8 | 1 | 1 | 10 | 7.8 | N/A |
| 79 | 7.9 | 1 | 1 | 10 | 7.9 | N/A |
| 80 | 8.0 | 2 | 2 | 20 | 4.0 | 4.0 |

| Body Weight (kg) | DDFPe Dose 0.10mL/kg | Number of DDFPe 10mL Vials Required | Number of 10mL Syringes to be Prepared | Total Volume to be Prepared (mL) | Volume to be Administered from 1st syringe (mL) | Volume to be Administered from 2nd Syringe (mL) |
|---|---|---|---|---|---|---|
| 81 | 8.1 | 2 | 2 | 20 | 4.1 | 4.0 |
| 82 | 8.2 | 2 | 2 | 20 | 4.2 | 4.0 |
| 83 | 8.3 | 2 | 2 | 20 | 4.3 | 4.0 |
| 84 | 8.4 | 2 | 2 | 20 | 4.4 | 4.0 |
| 85 | 8.5 | 2 | 2 | 20 | 4.5 | 4.0 |
| 86 | 8.6 | 2 | 2 | 20 | 4.6 | 4.0 |
| 87 | 8.7 | 2 | 2 | 20 | 4.7 | 4.0 |
| 88 | 8.8 | 2 | 2 | 20 | 4.8 | 4.0 |
| 89 | 8.9 | 2 | 2 | 20 | 4.9 | 4.0 |
| 90 | 9.0 | 2 | 2 | 20 | 5.0 | 4.0 |
| 91 | 9.1 | 2 | 2 | 20 | 5.1 | 4.0 |
| 92 | 9.2 | 2 | 2 | 20 | 5.2 | 4.0 |
| 93 | 9.3 | 2 | 2 | 20 | 5.3 | 4.0 |
| 94 | 9.4 | 2 | 2 | 20 | 5.4 | 4.0 |
| 95 | 9.5 | 2 | 2 | 20 | 5.5 | 4.0 |
| 96 | 9.6 | 2 | 2 | 20 | 5.6 | 4.0 |
| 97 | 9.7 | 2 | 2 | 20 | 5.7 | 4.0 |
| 98 | 9.8 | 2 | 2 | 20 | 5.8 | 4.0 |
| 99 | 9.9 | 2 | 2 | 20 | 5.9 | 4.0 |
| 100** | 10.0 | 2 | 2 | 20 | 5.0 | 5.0 |

Total DDFPe Dose = 0.10 mL/kg x weight in kg.
*Minimum subject weight = 45 kg.
**Maximum subject weight used for dose calculation = 100 kg. For subjects weighing more than 100 kg, dose will be calculated based on a weight of 100 kg.

DDFPe dosage volume in cc for **0.17 mL/kg** based on patient body weight in kilograms (kg).

| Body Weight (kg) | DDFPe Dose 0.17mL/kg (mL) | Number of DDFPe 10mL Vials Required | Number of 10mL Syringes | Total Volume to be Prepared (mL) | Volume to be Administered from 1st syringe (mL) | Volume to be Administered from 2nd syringe (mL) | Volume to be Administered from 3rd syringe (mL) |
|---|---|---|---|---|---|---|---|
| 45* | 7.6 | 1 | 1 | 10 | 7.6 | N/A | N/A |
| 46 | 7.8 | 1 | 1 | 10 | 7.8 | N/A | N/A |
| 47 | 8.0 | 1 | 1 | 10 | 8.0 | N/A | N/A |
| 48 | 8.2 | 1 | 1 | 10 | 8.2 | N/A | N/A |
| 49 | 8.3 | 1 | 1 | 10 | 8.3 | N/A | N/A |
| 50 | 8.5 | 1 | 1 | 10 | 8.5 | N/A | N/A |
| 51 | 8.7 | 1 | 1 | 10 | 8.7 | N/A | N/A |
| 52 | 8.8 | 1 | 1 | 10 | 8.8 | N/A | N/A |
| 53 | 9.0 | 2 | 2 | 20 | 4.5 | 4.5 | N/A |
| 54 | 9.2 | 2 | 2 | 20 | 4.6 | 4.6 | N/A |
| 55 | 9.4 | 2 | 2 | 20 | 4.7 | 4.7 | N/A |
| 56 | 9.5 | 2 | 2 | 20 | 4.8 | 4.7 | N/A |
| 57 | 9.7 | 2 | 2 | 20 | 4.9 | 4.8 | N/A |
| 58 | 9.9 | 2 | 2 | 20 | 5.0 | 4.9 | N/A |
| 59 | 10.0 | 2 | 2 | 20 | 5.0 | 5.0 | N/A |
| 60 | 10.2 | 2 | 2 | 20 | 5.1 | 5.1 | N/A |
| 61 | 10.4 | 2 | 2 | 20 | 5.2 | 5.2 | N/A |
| 62 | 10.5 | 2 | 2 | 20 | 5.3 | 5.2 | N/A |
| 63 | 10.7 | 2 | 2 | 20 | 5.4 | 5.3 | N/A |
| 64 | 10.9 | 2 | 2 | 20 | 5.5 | 5.4 | N/A |
| 65 | 11.0 | 2 | 2 | 20 | 5.5 | 5.5 | N/A |
| 66 | 11.2 | 2 | 2 | 20 | 5.6 | 5.6 | N/A |
| 67 | 11.4 | 2 | 2 | 20 | 5.7 | 5.7 | N/A |
| 68 | 11.6 | 2 | 2 | 20 | 5.8 | 5.8 | N/A |
| 69 | 11.7 | 2 | 2 | 20 | 5.9 | 5.8 | N/A |
| 70 | 11.9 | 2 | 2 | 20 | 6.0 | 5.9 | N/A |
| 71 | 12.1 | 2 | 2 | 20 | 6.1 | 6.0 | N/A |
| 72 | 12.2 | 2 | 2 | 20 | 6.1 | 6.1 | N/A |
| 73 | 12.4 | 2 | 2 | 20 | 6.2 | 6.2 | N/A |
| 74 | 12.6 | 2 | 2 | 20 | 6.3 | 6.3 | N/A |
| 75 | 12.8 | 2 | 2 | 20 | 6.4 | 6.4 | N/A |
| 76 | 12.9 | 2 | 2 | 20 | 6.5 | 6.4 | N/A |
| 77 | 13.1 | 2 | 2 | 20 | 6.6 | 6.5 | N/A |
| 78 | 13.3 | 2 | 2 | 20 | 6.7 | 6.6 | N/A |
| 79 | 13.4 | 2 | 2 | 20 | 6.7 | 6.7 | N/A |
| 80 | 13.6 | 2 | 2 | 20 | 6.8 | 6.8 | N/A |

| Body Weight (kg) | DDFPe Dose 0.17mL/ kg (mL) | Number of DDFPe 10mL Vials Required | Number of 10mL Syringes | Total Volume to be Prepared (mL) | Volume to be Administered from 1st syringe (mL) | Volume to be Administered from 2nd syringe (mL) | Volume to be Administered from 3rd syringe (mL) |
|---|---|---|---|---|---|---|---|
| 81 | 13.8 | 2 | 2 | 20 | 6.9 | 6.9 | N/A |
| 82 | 13.9 | 2 | 2 | 20 | 7.0 | 6.9 | N/A |
| 83 | 14.1 | 2 | 2 | 20 | 7.1 | 7.0 | N/A |
| 84 | 14.3 | 2 | 2 | 20 | 7.2 | 7.1 | N/A |
| 85 | 14.4 | 2 | 2 | 20 | 7.2 | 7.2 | N/A |
| 86 | 14.6 | 2 | 2 | 20 | 7.3 | 7.3 | N/A |
| 87 | 14.8 | 2 | 2 | 20 | 7.4 | 7.4 | N/A |
| 88 | 15.0 | 2 | 2 | 20 | 7.5 | 7.5 | N/A |
| 89 | 15.1 | 2 | 2 | 20 | 7.6 | 7.5 | N/A |
| 90 | 15.3 | 2 | 2 | 20 | 7.7 | 7.6 | N/A |
| 91 | 15.5 | 2 | 2 | 20 | 7.8 | 7.7 | N/A |
| 92 | 15.6 | 2 | 2 | 20 | 7.8 | 7.8 | N/A |
| 93 | 15.8 | 2 | 2 | 20 | 7.9 | 7.9 | N/A |
| 94 | 16.0 | 2 | 2 | 20 | 8.0 | 8.0 | N/A |
| 95 | 16.2 | 3 | 3 | 30 | 6.0 | 6.0 | 4.2 |
| 96 | 16.3 | 3 | 3 | 30 | 6.0 | 6.0 | 4.3 |
| 97 | 16.5 | 3 | 3 | 30 | 6.0 | 6.0 | 4.5 |
| 98 | 16.7 | 3 | 3 | 30 | 6.0 | 6.0 | 4.7 |
| 99 | 16.8 | 3 | 3 | 30 | 6.0 | 6.0 | 4.8 |
| 100** | 17.0 | 3 | 3 | 30 | 6.0 | 6.0 | 5.0 |

Total DDFPe Dose = 0.17 mL/kg x weight in kg.
*Minimum subject weight = 45 kg.
**Maximum subject weight used for dose calculation = 100 kg. For subjects weighing more than 100 kg, dose will be calculated based on a weight of 100 kg.

**Appendix 3**: **Modified Rankin Scale**

**Subject Name:** _____
**Rate Name:** _____
**Date:** _____

Scale to be administered as part of the exclusion criteria and again at follow up (discharge and end of study)

| SCORE | DESCRIPTION |
|---|---|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Moderate disability; requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing attention |
| 6 | Dead |

Score (0-6): _____

**References**

Rankin J. Cerebral vascular accidents in patients over the age of 60. Scot Med J 1957;2:200-215.

Bonita R, Beaglehole R. Modification of Rankin Scale: Recovery of motor function after stroke. Stroke 1988;19(12):1497-1500.

## Appendix 4: Schedule of Time and Events

| | **Day 1** | | | | | **Day 4** | **Day 7±1 or Day of Discharge** | **Day 30 ±7** | **Day 90 ±14** |
|---|---|---|---|---|---|---|---|---|---|
| Study Procedures | Screening (Baseline) | Dose #1[a] | Dose #2[a] | Dose #3[a] | Post-Dose #3[b] | | | | |
| Informed Consent | X | | | | | | | | |
| I/E Criteria | X | | | | | | | | |
| Concomitant Meds | X | X | X | X | X | | | | |
| Medical History[c] | X | | | | | | X | X | X |
| Physical Exam[c] | X | | | | X | | X | X | |
| Weight | X | | | | | | | | |
| Vital Signs[d] | X | X | X | X | X | | X | X | |
| Pulse Oximetry[e] | X | X | X | X | X | | X | | |
| Modified Rankin Scale | X | | | | | | X | X | X |
| NIHSS | X | | X[f] | X[f] | X | | X | X | |
| ECG[g] | X | | | | X | | X | | |
| Pregnancy Test[h] | X | | | | | | | | |
| Lab Studies[i] | X | | | | X | | X | | |
| Administer DDFPe[j] | | X | X | X | | | | | |
| Adverse Events | | X | X | X | X | X | X | X | X |

a Each dose of DDFPe or placebo is to be administered intravenously over 5-10 minutes. Start and stop times will be recorded as will the volume infused.
b Post-dose #3 concludes approximately 4-6 hours after the end of the Dose #3 infusion.
c Brief, targeted medical history and physical exam.
d Vital signs (blood pressure, heart rate, respiratory rate) will be done every 15 minutes through the end of Post-Dose #3 (approximately 4-6 hours) and then consistent with standard procedures for the hospital unit. Temperature will be done every 1-4 hours consistent with the hospital unit standard procedures.
e Continuous or spot readings may be taken; if continuous readings are used, record the measurement every 15 minutes.
f To be performed within 60 minutes following the dose.
g 12-lead ECG to be examined at the bedside by the study personnel and later reviewed by a board certified cardiologist.
h Serum pregnancy test will be done in pre-menopausal women.
i To include: CBC, electrolytes (Na, K, Cl,), BUN, creatinine, LFTs, calcium, albumin, glucose
j DDFPe or placebo to be administered over 5-10 minutes intravenously through a peripheral or central IV. The interval between the end of one dose and the beginning of the next should be 90 ± 10 minutes.