Chapter 11.0: Protocol

CLEAR III

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III

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IND:	8523
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AGREEMENT ON THE PROTOCOL

Trial ID: **CLEAR III**
Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III
NIH/NINDS
IND #: 8523

The Principal Investigator (hereafter referred to as Investigator) and The Johns Hopkins Medical Institutions (hereafter referred to as JHMI) agree to conduct the trial as outlined in this protocol with reference to national/local/international regulations and in accordance with current *Good Clinical Practice* (GCP) and *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH).

Any modification to the protocol must be agreed upon by both the Investigator and JHMI and documented in writing. By written agreement to this protocol, the Investigator agrees to allow direct access to all documentation, including source data, to authorized individuals representing JHMI (including monitoring staff and auditors), to Institutional Review Boards (IRB) and/or to regulatory authorities.

Signature: _____ Date: _____

Name Printed: _____

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List of Abbreviations:

AANS	American Association of Neurological Surgeons
AE	Adverse Event
AHA	American Heart Association
AHFS	American Hospital Formulary Service
AMI	Acute Myocardial Infarction
APTT	Activated Partial Thromboplastin Time

ASA	American Stroke Association
BP	Blood Pressure
BPM	Beats per Minute
C	Celsius
CBC	Complete Blood Counts
cc	Cubic Centimeters
CD	Compact Disc
CFR	Code of Federal Regulations
CI	Confidence Interval
CLEAR III	Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III
CPP	Cerebral Perfusion Pressure
CRF	Case Report Forms
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CV	Cardiovascular
DBP	Diastolic Blood Pressure
D/C	Discharge
DCR	Data Clarification Request
DHHS	Department of Health and Human Services
DOB	Date of Birth
DSMB	Data Safety and Monitoring Board
DVT	Deep Vein Thrombosis
EC	Ethics Committee
EC	Executive Committee
eCRF	Electronic Case Report Form
EDA	Exploratory Data Analysis
EDC	Electronic Data Capture
ETOH	Alcohol
EVD	Extraventricular Drainage
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GCS	Glasgow Coma Scale
GEE	Generalized Estimating Equations
GLMM	Generalized Linear Mixed Models
GOS	Glasgow Outcome Scale
HRQOL	Health-Related Quality of Life
HIPAA	Health Insurance Portability and Accountability Act
h or hrs	Hours
IB	Investigator's Brochure
ICH	Intracerebral Hemorrhage
ICH	International Conference on Harmonization
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IND	Investigational New Drug

INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IU	International Units
IV	Intravenous
IVC	Intraventricular Catheter
IVH	Intraventricular Hemorrhage
JHU	Johns Hopkins University
kg	Kilogram
LOC	Level of Consciousness
LOS	Length of Stay
LTFU	Lost to Follow Up
min	Minute
mg	Milligram
mL	Milliliter
mm	Millimeters
mmHg	Millimeters of Mercury
MOP	Manual of Operations and Procedures
MRA	Magnetic Resonance Angiogram
MRC	Medical Research Council of Great Britain
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
ng	Nanograms
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
OHRP	Office of Human Research Protection
OR	Odds Ratio
PBSI	Preference Based Stroke Index
PHM	Proportional Hazards Model
PI	Package Insert
PK	Pharmacokinetics
PT	Prothrombin time
q	Every
QD	Every day
QOL	Quality of Life
RCT	Randomized Clinical Trial
RDE	Remote Data Entry
RE	Random Effects
rt-PA	Recombinant Tissue Plasimogen Activator
s	Seconds
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SBP	Systolic Blood Pressure
SD	Standard Deviation
SID	Study Identification Number

SIS	Stroke Impact Scale
SOC	Standard of Care
STICH	The Surgical Trial in ICH
SQL	Structured Query Language
TBD	To Be Determined
TIL	Treatment Intensity Level
UK	Urokinase
μmg	Microgram
US	United States
USP	United States Pharmacopoeia
VP	Ventriculoperitoneal
WIRB	Western Institutional Review Board

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11.1 Introduction

11.1.1. Study Title

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR III)

11.1.2. Objectives

Primary objectives: To define precisely the long-term effects of lysing ventricular blood clots with rt-PA on the functional outcomes of cerebral hemorrhage patients. We propose to test if this intervention promotes a recovery of function, as defined as a modified Rankin score of ≤ 3 at 180 days post ictus, by facilitating more rapid clot resolution as compared to treatment with extraventricular drainage (EVD) with placebo.

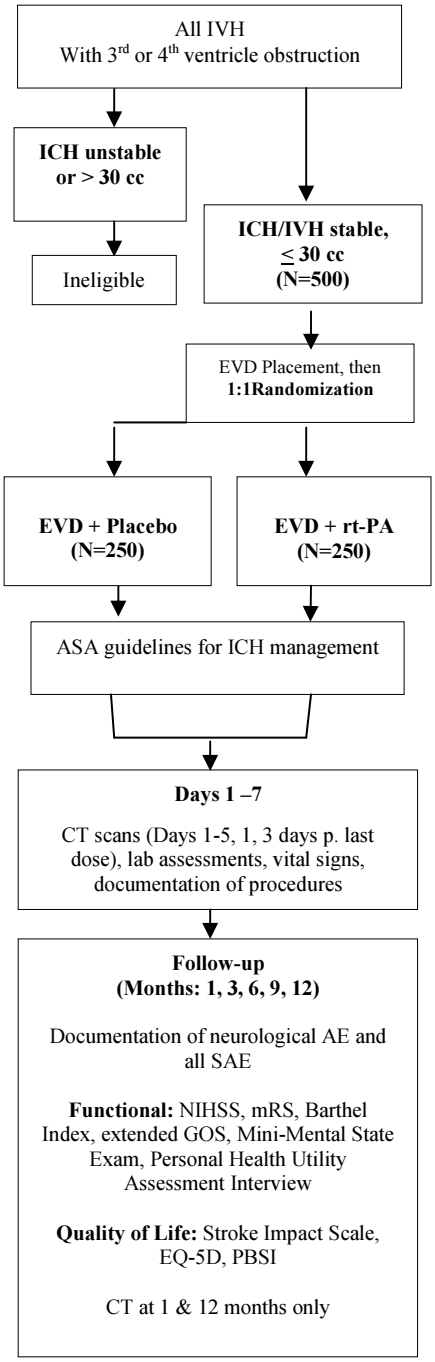
Secondary objectives: To test if mortality at 180 days is improved for subjects receiving rt-PA, if the amount of residual blood at 72 h correlates directly with the functional outcome at 180 days post bleed, and if rt-PA use in IVH patients leads to less intense ICU management, including fewer ICU days, shorter periods of CSF drainage, decreased intensity of ICP management, lower rate of needing permanent ventriculoperitoneal shunt, and fewer general critical care complications.

11.1.3. Design and Outcomes

This study is a multicenter, international, double-blind, randomized study comparing the use of EVD combined with rt-PA against EVD combined with placebo for the treatment of intraventricular hemorrhage.

11.1.4. Interventions and Duration

The intervention to be compared is EVD + rt-PA against EVD + placebo (normal saline). In the EVD + rt-PA group, a low dose (1.0 mg q 8 hours) of the thrombolytic rt-PA will be administered via an EVD to the intraventricular clot. This will be performed as intermittent, isovolumetric injections of 1.0 mg of Cathflo® followed by up to 4.0 ml of flush (normal saline) given every 8 hours for up to 12 doses. Placebo patients will receive 1.0 mL of sterile normal saline given every 8 hours for up to 12 doses.



All randomized subjects will undergo CT scans daily through day 5 and again 1 and 3 days (approximately 24 and 72 hours) post last dose of test article. Vital signs collection begins at enrollment and is done every 4 hours through day 7. Vital signs include blood pressure, heart rate, temperature, ICP (also CPP and MAP calculated by eCRF), drip chamber height, Glasgow Coma Scale score, treatment

intensity levels (TILs), and cerebrospinal fluid drainage amount and management. ICP data will be collected retrospectively back to the first IVC placement and prospectively from enrollment through day 7. Beginning with day 8 and ending with the removal of the last IVC placed, a once daily assessment of ICP, total CSF drainage, and drip chamber height will be collected retrospectively at the 30 day follow-up visit or sooner. Follow up visits will be performed at 1, 3 (phone), 6, 9 (phone), and 12 months post diagnosis. All follow up clinic visits (1, 6, and 12 months) include NIHSS, extended Glasgow Outcome Scale, video-taped modified Rankin Scale, Barthel Index, Stroke Impact Scale, Mini-Mental exam, EQ-5D, Preference-Based Stroke Index, blood pressure monitoring, documentation of neurological adverse events or any serious adverse events related to study treatment since last visit, and a CT scan (at the 1- and 12-month visits only). The Personal Health Utility Assessment Interview will be done at the 6 month clinic visit. Follow up phone visits (3 and 9 months) include Barthel Index, EQ-5D, Preference-Based Stroke Index, and documentation of neurological adverse events or any serious adverse events related to study treatment since last visit.

11.1.5. Sample Size

Approximately 500 patients with onset of intraventricular hemorrhage will be randomized between EVD management with rt-PA or placebo. All patients will receive external ventricular drainage, prior to randomization, via placement of an intraventricular catheter when indicated by neurosurgical standard of care.

11.2. STUDY OBJECTIVES

11.2.1. Primary Objective

We propose to define precisely the long-term effects of lysing ventricular blood clots with rt-PA on the functional outcomes of cerebral hemorrhage patients presenting with severe IVH. We propose to test if facilitating more rapid clot resolution by clot drainage plus rt-PA promotes a recovery of function as defined as a modified Rankin score of ≤ 3 at 180 days post ictus.

11.2.2. Secondary Objectives

To determine if patients receiving EVD + rt-PA in contrast to patients receiving EVD + placebo attain better scores on the secondary measures of efficacy, which include the mRS score on the ordinal (0-6) scale as well as the 0-4 vs 5,6 dichotomy, mortality at 180 days post treatment, amount of residual blood at 72 hours, rate of blood removal, intensity of critical care management as measured by length of ICU stay, duration of EVD, intensity of ICP management, and frequency of critical care complications. Measures of functional outcome and quality of life will include: the modified Rankin Scale, the Barthel Index, the EQ-5D, and the total time at home after ICH at months 1, 3, 6, 9, and 12. In addition, extended Glasgow Outcome Scale, the Stroke Impact Scale, the NIHSS, the Mini-Mental State Exam, and the Preference-Based Stroke Index will be done, and the modified Rankin Scale will be videotaped, at 1, 6, and 12 month clinic follow-up visits.

11.3. Background Information

11.3.1. Rationale

The study population will include approximately 500 patients across 75 study centers located in the US, Canada, Europe, and South America. Eligible patients will have intraventricular hemorrhage without

suspected underlying structural etiology (tumor, vascular malformation or aneurysm). Patients will be identified and recruited through the clinical stroke service in emergency settings and as direct admissions to the Neurocritical Care/Stroke Units at each study center.

IVH occurs in about 40% of primary intracerebral hemorrhage (ICH) and 15% of aneurysmal subarachnoid hemorrhage (SAH).[1-4] The incidence of IVH in ICH is about twice that of SAH; respectively, they account for about 10% and 5% of the 500,000 new strokes occurring yearly in the U.S,[2, 5] translating to about 22,000 people per year with an IVH. Most recent research supports the assertion that IVH is a significant and independent contributor to morbidity and mortality in both.[1, 3, 6-12] Mortality estimates for this condition are from 40-80%.[9, 13] Recently, two large randomized clinical trials (RCT), with well-established monitoring and adjudication mechanisms, have demonstrated the importance of IVH as a severity factor. The Surgical Trial in ICH (STICH) trial, an international effort funded by the Medical Research Council of Great Britain (MRC), enrolled 964 ICH patients to test the value of early surgery vs. medical management. Ventricular extension occurred in 42%; hydrocephalus occurred in 55% of these. IVH with and without hydrocephalus were strongly associated with poor outcome: whereas 31% without IVH had good outcome, only 15% with IVH experienced good outcome ($p<0.00001$). When IVH and hydrocephalus were combined, good outcome fell to 11%[14] Similarly, IVH occurred in 49% of all patients enrolled in the NovoSeven ICH trial (n=399). Modified Rankin scores were consistently worse in this group of patients[15] Although IVH severely complicates a large percentage of ICH patients, little organized clinical research has been directed at improving the management of IVH, including the use of EVDs. This proposal is directed specifically to explore the possibility that amelioration of IVH benefits ICH patients.

Pathophysiology and present clinical management of IVH. Intraventricular hemorrhage contributes to morbidity in three ways. First, IVH organizes into ventricular blood clots, which then block the narrow ventricular CSF conduits, producing acute obstructive hydrocephalus. If untreated, obstructive hydrocephalus invariably elevates intracranial pressure (ICP) and, as the increased ICP approaches the arterial perfusion pressure, can quickly progress to death. After IVH, obstructive hydrocephalus is the greatest and most immediate threat to life. Present treatment of IVH-associated obstructive hydrocephalus is to use EVD through an intraventricular catheter (IVC). EVD lowers ICP immediately, but it must be continued until the ventricular blood clots have dissolved sufficiently and CSF circulation is normalized. To date, the role of direct mass effect from ventricular distention has not been well defined. Clinically, controlling ICP does not usually improve the patient immediately.[13] Thus, direct mass effect of IVH may be a significant pathophysiologic event independent of the ICP elevation.

Second, prolonged presence of IVH clot deep within the brain is associated with both mortality[13, 16, 17] and decreased level of consciousness.[18, 19] EVD does not consistently improve either one. It does not alter either ventricular size, edema, or the inflammation provoked by the presence of intraventricular blood.[20] EVD does not change the time required for blood clot resolution.[21] Indeed, EVD may worsen this edema and inflammation because it is frequently complicated by meningitis. Until now, reducing the size of the intraventricular clot and decreasing the time that deep brain structures are exposed to clot have not been directly addressed by any current IVH treatment.

Third, blood degradation products carried to the arachnoid granulations by the CSF flow may contribute to morbidity. With prolonged contact between blood degradation products and the arachnoid, the

ensuing inflammatory response may permanently occlude and scar the arachnoid granulations where CSF is absorbed.[22-25] These occlusions in the arachnoid granulations gradually produce delayed communicating hydrocephalus, which, in turn, impairs cognition, gait and balance, and urinary continence. Patients with communicating hydrocephalus require permanent implantation of a shunt for CSF diversion.

Four prognostic studies have demonstrated the independent effect of IVH on mortality.[8, 9, 26, 27] Most recently, a prospective evaluation of ICH patients demonstrated a direct, continuous, dose-effect relationship between volume of IVH and mortality.[27] No such data exist for SAH or primary IVH populations. ICH can occur in many cerebral locations and has many distinct sizes, but despite well-known relationships between ICH location and neurologic deficits and disabilities, no clear relationship exists between ICH location and mortality.[8, 26, 27] ICH volume also relates to mortality. There is an incremental, direct relationship of volume to mortality for ICH volumes greater than 30 cc. A volume size of 30 cc appears to be the threshold, below which mortality is a low frequency event (about 20%)[26] Currently, all available data support the concept that mortality in small ICH (<30 cc) with IVH extension is in large part related to the IVH.[27] We believe that minimizing variability and excluding large ICH volumes on enrollment will allow for the selection of patients with a uniform disease severity. A uniform population will allow us to test the hypothesis that IVH is a reversible injurious factor, which if remedied, will alter mortality.

Problems with present clinical management of IVH. *a) EVD alone is often inadequate therapy for obstructive hydrocephalus.* Although intended to treat obstructive hydrocephalus, EVD is often inadequate in the setting of IVH because the catheter becomes occluded with blood clots. Conventional therapy for catheter occlusion with blood is removal of the occluded catheter and insertion of a second catheter in another location, preferably one that is free of blood. Relocation of the IVC carries about a 1% risk of intracranial hemorrhage,[28, 29] and is often unsuccessful because only a portion of the ventricles can be reliably accessed by an IVC. If the accessible portion is occupied by blood, the new IVC will likely occlude. Thus for many patients, EVD is unsuccessful and they succumb to inadequately treated obstructive hydrocephalus. Even when obstructive hydrocephalus is amenable to EVD, persistent blood clots increase the time that drainage is needed, thus increasing the risk of ventriculitis. The risk of ventriculitis from infection is about 10% to 20% and appears to be directly related to duration of IVC placement.[30-32]

b) External ventricular drainage does not speed clot resolution. External ventricular drainage of CSF is indicated in patients with IVH to relieve any associated hydrocephalus. EVD cannot, however, remove the clot or relieve local tissue compression from distended ventricles. EVD does not alter the rate of blood clot resolution.[33] Although helpful in controlling increased ICP until the occluding clots are cleared in the CSF conduits by the patient's own clearance mechanism, EVD does not shorten the time that the blood clot is in contact with the ventricular system and deep brain structures. Thus, EVD alone does not alter the impact of intraventricular clot on deep brain tissue.

c) EVD fails to decrease the degree and incidence of communicating hydrocephalus. Since EVD does not hasten the resolution of the intraventricular blood clot, it does little to prevent the later pathophysiologic consequence of IVH — communicating hydrocephalus. Delayed communicating hydrocephalus is caused by an inflammatory reaction generated by the break down of blood products,[22-

[25] the intensity of which appears to be related to the amount of blood present and the time that the CSF is exposed to the clotted blood.[34-39] Development of communicating hydrocephalus often is associated with cognitive impairment, urinary incontinence, and gait and balance problems. This requires surgery for shunt insertion, leaving the patient with the lifelong risk of shunt occlusions and infections.

Clearly, any adjuvant therapy that could accelerate the resolution of the blood clot and thus reduce the clot-related pathological events would be a major advance and potential lifesaver in the clinical management of IVH. Intraventricular thrombolysis is an obvious candidate therapy to fulfill these adjuvant requirements, as an animal model demonstrated both amelioration of inflammation and substantial protection from delayed hydrocephalus.[16, 18]

Choice of Thrombolytic and Dose. In a previous clinical trial, a dose of 3.0 mg every 12 hours was used as the initial baseline dose to test safety for the following reasons. No studies have evaluated the kinetics of rt-PA activity in the normal human CSF. Indeed such a study cannot be ethically performed in an individual without disease-related access to ventricular CSF. Animal model data have not been available to definitively establish dose. The best available animal study of intraventricular thrombolysis was performed by Pang et al.,[37,39] in which 20,000 IU of urokinase was administered every 12 hours until evidence of clot resolution was obtained. The clots treated in that study had a mean volume of 6.9 cc;[38] clots that were present in the patients with IVH in our natural history study (n = 17) who had treatment with EVD (n=9, 53%) had a mean volume of 38.6 cc. Although it is difficult to translate dosing in the canine model to this study, the proposed doses appear to be conservative, given the differences in clot volumes expected to be treated. The proposed doses are also within the range of dosages reported in the clinical series cited previously,[2,12,13,30,44,48,50] none of which reported substantial rates of hemorrhagic complications. The proposed doses are also significantly less than the recommended dose for use in acute ischemic stroke (0.9 mg/kg intravenously over 1 hour; not to exceed 90 mg for a 70-kg adult). The usual dose of rt-PA for coronary artery thrombolysis is 100 mg IV (AHFS Drug Information) while the usual dose of urokinase for coronary artery thrombolysis is 500,000 to 1,000,000 IU.[27,28] This implies an approximate efficacy ratio of 1.0 mg of rt-PA to 5,000-10,000 IU of urokinase for coronary thrombolysis.

The half-life of rt-PA in the CSF or the ventricles is currently undefined. It is unknown whether rt-PA is totally and immediately bound to fibrin clot or whether free rt-PA exists for some time after administration in the ventricular system. Since bulk CSF flow is much slower than blood flow, the CSF half-life is probably significantly longer than the 26.5-minute half-life in the terminal elimination phase of rt-PA from the peripheral arterial circulation, but it is almost certainly much shorter than the 12-hour dosing regimen we have previously used (AHFS Drug Information). A study of rt-PA half-life in the CSF was performed in subarachnoid hemorrhage patients not dissimilar to our IVH patients and demonstrated a half-life of 2 to 3 hours.[56]

Pharmacokinetics (PK) data. The optimal local dose of rt-PA for effective intervascular clot lyis is thought to be 6,000 ng/mL. Thus the PK results will be important to the decision of which dose to select. ***We have evaluated three different doses including 0.3, 1.0, and 3.0 mg administered intraventricularly and found from both a pharmacokinetic and safety/efficacy standpoint that 1.0 mg appeared to be the optimal dose*** (DF Hanley. Intraventricular Hemorrhage. Severity Factor and Treatment Target in Spontaneous Intracerebral Hemorrhage. Stroke. 2009;40:1533.)**.** The difference in

peak concentrations of the 3.0 mg dosing group was significantly higher than the other dosing regimens and exceeded 6,000 ng/mL by 100% to 1000% while the 0.3 mg frequently did not achieve this concentration. The median peak concentration of the 1.0 mg dosing group was 13,827 ng/mL. The calculated half-life of all dosing groups ranged from 2.5 to 3.2 hours with the largest drop in concentration occurring after opening the intraventricular catheter. The trough concentrations of all doses were below the 6000 ng/mL target and in fact concentrations only remained above this target for 20 to 25% of the dosing interval. Our data also shows evidence of CSF thrombolysis reflected in the drop in plasminogen by 34-53% of baseline following rt-PA administration and an increase in CSF fibrin degradation products of 35-44% following rt-PA. When evaluating the shortening of the dosing interval from 12 to 8 hours we found no increased accumulation of rt-PA. Our data show that catheter opening plays an important role in intraventricular rt-PA elimination. Based upon all available data we feel confident that 1.0 mg provides the safest most effective dose. A detailed rationale for the selection of the 1.0 mg dose is available in Appendix 1.

Drug delivery. The optimal method of delivering a drug with a short half-life is by constant infusion, which is used most often for rt-PA in the peripheral and coronary circulation (AHFS Drug Information), and which has been tested for safety. Constant infusion of any agent into the CSF or ventricular system, however, poses several obstacles. The risk of ventriculitis and cerebritis could be increased by a constant infusion versus an intermittent injection; the infusion rate would have to be extremely slow to avoid raising the ICP; and the rate of the infusion due to pump malfunction or human error would need to be monitored. Thus, intermittent injections appear to be the simplest route of administration. The optimal interval between injections is unknown. The worthwhile attempt to achieve a constant state of drug saturation with more frequent injections must be balanced by the risk of a catheter-related infection, which is increased by the number of times the catheter is manipulated.[32] The dosing interval of 12 hours balanced potential efficacy against the most frequent complication, infection. Stage 2 shortened the time interval between doses to test more closely for the administration paradigm that is theoretically optimal to achieve rapid clot lysis. The results from Stage 2 of the CLEAR IVH trial demonstrate a dose response relation between opening of the 3rd and 4th ventricles and doses between 0.3 mg q 12 hours, 1.0 mg q 12 hours, and 1.0 mg q 8 hours. Additionally the safety profile of low (8%) symptomatic bleeding and low ventriculitis (8%) was maintained in Stage 2. These data continue to support the need for a paradigm that produces this goal of clot size reduction in the first days after IVH. Thus the explicit goal of achieving 80% IVH clot lysis by 72 hours of rt-PA administration remains an important secondary aim of this treatment. Because the study is limited to four (or less) days, the total number of ventriculostomy openings will be similar to those in the completed safety study, which had a 6.7% rate of ventriculitis. No increase in risk of infection is anticipated in Phase III.

11.3.2. Supporting Data

This study is designed to compare the ability of EVD in combination with recombinant tissue plasminogen activator (rt-PA; Alteplase) to EVD in combination with placebo to restore functional outcome at 180 days post onset of intraventricular hemorrhage (IVH). The principal investigator holds an IND for clot lysis with this drug specific to this protocol (IND #8523).

Drug Biochemistry and Formulation. Tissue plasminogen activator as found in tissue or in the melanoma cell line is a serine protease glycoprotein varying in molecular mass from 63,000 to 65,000 Daltons. The molecular mass variation reflects heterogeneity due to different patterns of

glycosylation. It contains an amino-terminal region that has a high degree of sequence homology with the "kringle" regions of plasminogen (Sottrup-Jensen et al. 1978) and prothrombin. A kringle is a characteristic triple disulfide structure originally described in the "pro" fragment of prothrombin (Magnusson et al. 1975). The amino-terminal region may be responsible for the fibrin-specific activation of t-PA. The carboxy-terminal end of the molecule contains a domain responsible for the protease activity of t-PA. t-PA is a mixture of one-chain and two-chain forms. The composition depends on the amount of proteolysis that takes place during manufacturing.

Current indications for drug use. Acute Myocardial Infarction (AMI). Alteplase is indicated for use in the management of AMI in adults for the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure, and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

Acute Ischemic Stroke. Alteplase is indicated for the management of acute ischemic stroke in adults for improving neurologic recovery and reducing the incidence of disability. Treatment should only be initiated within 3 hours after the onset of stroke symptoms and after exclusion of ICH by a cranial CT scan or other diagnostic imaging method sensitive for the presence of hemorrhage.

Pulmonary Embolism. Alteplase is indicated in the management of acute massive PE in adults: For the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs; for the lysis of pulmonary emboli accompanied by unstable hemodynamics (e.g., failure to maintain blood pressure without supportive measures); and the diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

11.3.3. Clinical and Non-Clinical Findings

Animal data

Current state of understanding regarding IVH thrombolysis. Pang et al. developed a model of IVH and intraventricular thrombolysis[16, 18] in which clotted blood was injected into the ventricles of adult dogs.[16] After determining, *in vitro,* the minimal dose of urokinase required to lyse 10 mL of clotted canine blood to be 10,000 IU, this dose was doubled and tested for safety *in vivo* by injecting 20,000 IU every 12 hours for 4 days into the ventricles of six adult dogs through an implanted ventricular catheter.[16] Rapid clearance of intraventricular blood occurred in the treated versus the control animals. With urokinase treatment all blood was removed before 1 week, the greater part of which occurred in the initial 2 to 3 days. [18] There were no intracranial or systemic hemorrhages and no chronic changes in the brain or meninges were demonstrated on histology sections at 3 months. In a pig model, Mayfrank showed prolonged ventricular dilatation and an association of blood clot volume with mass effect.[40] Significant decline in this mass effect was noted at 1.5 hours and 7 days when rt-PA was used for intraventricular thrombolysis. Importantly, in both canine and porcine models, the greater the volume of blood clot injected into the ventricles the greater the likelihood of animal death.[16, 40]

Effect of clot treatments on neurologic function. A direct effect of rapid reduction of clot size was shown in Pang's model in which he defined a canine consciousness score and applied it to urokinase

(UK)-treated and untreated dogs. When return-to-normal consciousness levels were assessed, two temporal groupings of dogs were distinguished. Two groups of clot resolution rates are also observed when clots from control and urokinase-treated dogs are compared. Early return of normal consciousness and more rapid removal of clot appear to be treatment-specific effects in this model.[94]

This controlled study then compared the rate of resolution of IVH between 10 untreated control dogs and 10 dogs treated with the regimen tested in the safety trial.[16] In the untreated dogs, complete lysis of the intraventricular blood clot required 38 to 65 days. Eight dogs developed hydrocephalus and had extensive ependymal and subependymal damage of the ventricular walls on histology section. In the treated dogs, the intraventricular blood clot was completely lysed in 3 to 6 days (SD = 5.2 $\pm$ 1.2) with no intracranial or systemic hemorrhages. The treated dogs promptly recovered neurological function, and only two developed hydrocephalus. Histology sections revealed no evidence of ventricular wall damage. Thus, in a canine model of IVH, Pang and co-workers demonstrated conclusively that intraventricular thrombolysis significantly hastened the resolution of the intraventricular blood clot, promoted rapid return of consciousness within 3 days, decreased the degree and incidence of delayed communicating hydrocephalus, and improved neurological outcome without damaging surrounding tissue.[16]

Human data

Safety of thrombolysis for IVH patients. Two members of our investigative group (Haines and Lapointe) reviewed the safety and efficacy of thrombolysis in the Cochrane collaboration format. This review defines the need for prospective studies. Case series experience with thrombolysis is as follows. In seven independent studies, the use of intraventricular thrombolytic agents has been reported in 74 patients with ICH or SAH.[41-47] Seventeen patients were treated with urokinase (12,000 IU to 96,000 IU daily) and 57 with rt-PA, 4 - 20 mg daily. Good neurological outcome was reported in 50 of the 74 patients as measured by each group's criteria; 22 of the 74 had long term follow-up, and of those, 8 developed delayed communicating hydrocephalus requiring permanent CSF diversion. Reported complications potentially attributable to treatment or EVD included: 5 cases of bacterial meningitis, 1 patient had an increase in hematoma volume[41],and 2 extradural hematomas were noted.[26] This safety profile suggests minimal side effects for low dose thrombolytic treatment.

Clinical experience with thrombolytic therapy for subarachnoid hemorrhage. There have also been several reports of intracisternal thrombolysis in the setting of SAH,[48-57] prompted by the hypothesis that hastening removal of blood clot from the intracisternal compartments will reduce the incidence of cerebral vasospasm. The most recent was a randomized trial comparing a single intraoperative dose of rt-PA against a placebo injection showed a trend toward a reduction in angiographic vasospasm. Safety was demonstrated by no significant difference in the bleeding complications between the treatment and placebo group.[48]

Clinical experience with anti-thrombolytic therapy for subarachnoid hemorrhage. The potential utility of thrombolytics in reducing the degree of communicating hydrocephalus is also supported by a study of intrathecal *anti-thrombolytic* therapy after aneurysmal SAH.[37] The authors reported the unanticipated finding that *anti-thrombolytic* therapy significantly increased the incidence of delayed

communicating hydrocephalus in comparison to the control group. Therefore, it is reasonable to hypothesize that *pro-thrombolytic* therapy could reduce the degree of communicating hydrocephalus.

Clot formation and clot dissolution. The target for our efforts is the brain's ventricular space. Much of what we know is derived from biochemical measurements of intravascular events that are similar. The normal vascular endothelium maintains blood fluidity by inhibiting blood coagulation and platelet aggregation and promoting fibrinolysis. The hemostatic system comprises a highly regulated series of procoagulant and anticoagulant zymogens and cofactors. Hemostasis (physiologic response to vascular injury) and thrombosis (pathological formation of thrombus) result from activation of this system. The balance between the coagulation cascade and the fibrinolytic pathway determines the rate of formation and dissolution of the thrombus. Blood coagulation and fibrinolysis are initiated and modulated by compounds embedded in the external membrane of cells (tissue factor, thrombomodulin), deposited in extra cellular matrix (heparin sulfate, dermatan sulfate, protease), or secreted by vascular cells in a regulated manner (von Willebrand factor, plasminogen activators, and plasminogen activator inhibitors).[58]

Preliminary data establish that exogenous administration of low dose rt-PA increases CSF rt-PA from inactive range to active fibrinolytic levels (i.e., > 6μmg/mL).[59] Concurrent increases in clot lysis products and reduction of clot size with computed tomography have now been demonstrated in treated patients.

Previous investigations of IVH thrombolysis by this investigative group. In-depth reporting of the results of each of the investigations described below can be found in Appendix 1.

Safety Study: The first study of IVH thrombolysis using rt-PA completed by this investigative group was a phase II, double-blind, randomized, safety study that evaluated 3.0 mg of rt-PA for clot lysis rate and safety. Patients were randomized to receive intraventricular injections of either 3.0 mg of rt-PA or placebo (normal saline) q 12hrs until complete IVH resolution, EVD removal, or a safety endpoint, whichever came first. The study started January 2000 and finished March 2003.

CLEAR IVH A: The second study was a double-blind, randomized dose finding study that evaluated two additional (lower) doses of rt-PA for clot lysis rate and safety. Patients were randomized to receive intraventricular injections of either 0.3 mg or 1.0 mg q 12hrs for up to eight doses or until the 3rd and 4th ventricles were open. The study started on February 2004 and finished on March, 2005. CLEAR IVH A was designed to test if new bleeding could be reduced with lower dose and when combined with improved stability standards. The 0.3 mg and 1.0 mg doses were associated with a reduction in hemorrhage rate to 0% (CI, 0-22%). This safety finding demonstrated our commitment to maximizing putative benefit while minimizing risk to participants.

CLEAR IVH B: The third study, an open-label dose escalation study evaluating 1.0 mg of rt-PA for clot lysis rate and safety, started August 2005 and completed enrollment on February 6, 2008. Patients were enrolled to receive intraventricular injections of 1.0 mg q 8hrs for up to twelve doses or until the 3rd and 4th ventricles were open. The CLEAR IVH B study was designed to use three tiers of 12 subjects to confirm the optimal frequency of the 1-mg dose and better define the confidence intervals of safety events and as well as develop data on long-term outcomes. The specific objectives of this trial were to

determine the shortest possible dose interval with the best pharmacokinetic and safety profile to remove significant amounts of blood clot from the ventricular system. In CLEAR IVH B, we tested the effect of shorter dose intervals (Q8-h vs. Q12-h) on clot resolution as determined by CT. To test for effect of drug delivery site on clot lysis, we compared total IVH Clot lysis rate (C_t) to rate of clot lysis in the 3rd and 4th ventricular regions ($C_{3,4}$). This cohort is the first where functional status was assessed after 30 days. The mRS assessments of the cohort of 36 subjects demonstrated an upward shift from more impaired to less impaired at 180 days. Thus, long term outcome shows sequential functional gain at day 180, with 30% of subjects achieving mRS 0-3.

Protocol similarities. The three previous clinical investigations of IVH thrombolysis using rt-PA all required clinical placement of the EVD for treatment of acute obstructive hydrocephalus, used q 8 to 12 hour drug administration regimen with one hour of EVD closure after each dose. Unlike the safety study patients, CLEAR IVH A and B patients were entered over a longer time window post bleed: up to 48 hours. American Stroke Association ICH guidelines and AANS ICP management guidelines continued to be the basis for establishing uniform critical care management of patients. Protocol additions used for the first time in CLEAR IVH A and B were: 1) Explicit process for clot measures at ICH and IVH sites needed for determination of 6 hour stability. 2) The use of a stability algorithm for assessment of EVD catheter track bleeds. 3) Explicit definition of drug termination criteria: (i.e., 3rd and 4th ventricular opening). Compliance with drug administration, CT acquisition and AANS ICP management guidelines was high.

Severity factor comparisons. Patient characteristics for the Safety Study, CLEAR IVH A, and CLEAR IVH B trials are displayed in the table below and show that the cohorts were similar in terms of gender, race, medical history, and intracerebral clot location.

Study	**CLEAR IVH A**				**CLEAR IVH B**		**Safety Study**		**Total**	
Dosage Volume	**0.3mg**		**1.0mg**		**1.0mg q8**		**3.0mg**		**Total**	
Variable	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Male	5	(62.5)	4	(50.0)	25	(69.4)	19	(73.1)	60	(60.0)
Female	3	(37.5)	4	(50.0)	11	(30.6)	7	(26.9)	40	(40.0)
Caucasian, not Hispanic	2	(25.0)	1	(31.8)	13	(12.5)	3	(36.1)	26	(26.0)
African American, not Hispanic	5	(62.5)	6	(45.5)	14	(75.0)	17	(38.9)	52	(52.0)
Hispanic	1	(12.5)	0	(0.0)	0	(0.0)	3	(11.5)	8	(8.0)
Asian / Pacific Islander	0	(0.0)	1	(12.5)	4	(11.1)	3	(11.5)	9	(9.0)
Other/unknown	0	(0.0)	0	(0.0)	5	(13.9)	0	(0.0)	5	(5.0)
Diabetes	1	(12.5)	0	(0.0)	10	(27.8)	6	(23.1)	20	(20.0)
Endocrine	2	(25.0)	1	(12.5)	7	(19.4)	8	(30.8)	22	(22.0)
CV	5	(62.5)	6	(75.0)	19	(52.8)	23	(88.5)	72	(72.0)
Hypertension	5	(62.5)	6	(75.0)	29	(80.6)	22	(84.6)	81	(81.0)
Stimulant Drug Use	3	(37.5)	2	(25.0)	4	(11.1)	3	(11.5)	14	(14.0)
ETOH / Drug Abuse	4	(50.0)	6	(75.0)	19	(52.8)	8	(30.8)	45	(45.0)
ETOH Abuse	2	(25.0)	3	(37.5)	2	(5.6)	6	(23.1)	19	(19.0)
Seizure	0	(0.0)	0	(0.0)	6	(16.7)	1	(3.8)	7	(7.0)
Angiogram	0	(0.0)	0	(0.0)	10	(27.8)	5	(19.2)	23	(23.0)
Clot Location										
Caudate	1	(12.5)	0	(0.0)	8	(22.2)	7	(26.9)	18	(18.0)
Thalamus	6	(75.0)	6	(75.0)	16	(44.4)	10	(38.5)	49	(49.0)
Putamen	0	(0.0)	0	(0.0)	1	(2.8)	3	(11.5)	7	(7.0)
Lobar	0	(0.0)	0	(0.0)	2	(5.6)	0	(0.0)	2	(2.0)

Globus Pallidus	0	(0.0)	0	(0.0)	1	(2.8)	2	(7.7)	3	(3.0)
Probable primary IVH	0	(0.0)	1	(12.5)	6	(16.7)	3	(11.5)	16	(16.0)
Not Given	1	(12.5)	1	(12.5)	2	(5.6)	1	(3.8)	5	(5.0)

Safety endpoint comparisons. Direct measurement of the initial clot lysis rate (first three days of treatment) demonstrated dose specific rates of 21.73%/day, 25.14%/day, 24.20%/day, and 19.98%/day for the 3.0 mg, 1.0 mg (q12hr), 0.3 mg, and 1.0 mg (q8hr) groups, respectively. The safety profile for the two lower doses was numerically superior to the 3.0 mg dose. Specifically no symptomatic bleeding occurred at either dose level (0.3 or 1.0). This trend continued in the CLEAR IVH B trial where the symptomatic hemorrhage rate is 8% after 36 patients. A blinded central analysis of C/D data did not demonstrate a significant difference in catheter tract bleeds between groups.

Study	Dosing Group	Subjects	30 Day Mortality # (%)	Symptomatic Bleeds # (%)	Bacterial Ventriculitis # (%)	Daily clot resolution rate
Safety Placebo (n=48)	3.0 mg q12h Placebo	22	5 (22.7%)	1 (4.5%)	2 (9.1%)	9.9%/day
	3.0 mg q12h rt-PA	26	5 (19.2%)	6 (23.1%)	2 (7.7%)	21.73%/day
CLEAR A (n=16)	0.3 mg q12h rt-PA	8	1 (12.5%)	0 (0%)	0 (0%)	25.14%/day
	1.0 mg q12h rt-PA	8	1 (12.5%)	0 (0%)	0 (0%)	24.20%/day
CLEAR B (n=36)	1.0 mg q8h rt-PA	36	7 (19.4%)	3 (8.3%)	1 (2.8%)	19.98%/day
Total		100	19 (19%)	10 (10%)	5 (5%)	

Gender appears to be associated with an increased baseline clot lysis rate and with a tendency to experience fewer clot enlargements/rebleeds. The 3.0 mg group had a male 73% to female 27% ratio compared to the CLEAR IVH A cohort of more women than men. Thus there is a possibility that the apparent improved safety profile is related to gender (greater number of women) or to the combination of small sample size and low intrinsic safety "event rates." Assessment for gender influence remains poorly powered because of small sample size. Final evaluation of gender for a population of 100 subjects suggests gender is not a major determinant of clot lysis rates. The Phase III trial will not include gender-specific dose adjustments.

Additionally, compared to the Safety Study, new protocol safety measures were instituted to better determine initial cessation of bleeding and to identify catheter tract enlargement early in its existence. Finally drug exposure was limited by total dose (only four days dosing allowed in CLEAR IVH A and B) and by explicit study termination criteria (opening of the 3rd and 4th ventricles), that when applied, led to earlier termination of study drug (i.e., decreased total drug doses) compared to the Safety Study. Longer periods of stabilization after EVD placement and now mandatory surveillance of catheter tract bleeding may have influenced the increased reporting of primary site rebleeding and catheter related bleeding, respectively. None of these factors are directly related to injected drug dose, but could partially or wholly account for the improved safety profile.

Ventricular clearance data. Because the drug administration protocol for CLEAR IVH A and B called for terminating drug delivery with opening of the 3rd and 4th ventricles, an analysis of the time to opening of these ventricles were informative with respect to dose selection. Such timing may not have as many biases related to catheter-clot anatomic relationships. This is important to note because the CLEAR IVH A and B protocols required placement near the third and fourth ventricles and required discontinuation of drug after clearance of these two sites. Thus the failure to lyse residual blood in the lateral ventricles is not taken into consideration with an evaluation focused solely on the 3rd and 4th ventricles. A blinded analysis of time to open these ventricles suggests the 1.0 and 3.0 mg doses trend toward more rapid and more complete opening.

A second factor possibly associated with variation of clot lysis rates is initial clot size. Inspection of the rt-PA treated clot lysis rates from each dose group suggests that smaller size IVH clots (i.e., < 50 cc) have faster lysis rates. This observation was recently made for the first time.

Potential Risks. The full risk profile and efficacy of this intervention are to be established in this Phase III study. Subjects randomized to EVD + rt-PA may have an increased risk of infection, hemorrhage extension, and new hemorrhage as compared to patients receiving EVD + placebo.

To minimize these risks, all subjects will be stabilized for at least 6 hours prior to the first dose of test article. All catheters will be inserted as standard of care and manipulated for drug administrations using the standard intensive care unit (ICU) infection risk-reduction protocol, and blood pressure will be controlled during the treatment period. The blood pressure goal should be to achieve and maintain a SBP > 90 and < 200 mmHg and a DBP of < 105 mmHg.

If at any time the rates of occurrence of 30-day survival fall below 40%, the bleeding event rate exceeds 25%, or the infection rate is greater than 20%, the DSMB will investigate the causes of these complications. If any of these complication rates are attributable to rt-PA injection at a 95% confidence level, the study will be suspended for a complete safety and efficacy review.

Potential Benefits. Analyses of previous safety studies' data suggest that mortality was improved for the overall study population but was not significantly different between the treatment groups. Patients receiving rt-PA had significantly faster daily clot resolution than those receiving placebo.

11.3.4. Background Literature and Data

Naff NJ, Williams MA, Rigamonti D**, Keyl PM, Hanley DF.** Blood clot resolution in human cerebrospinal fluid: evidence of first-order kinetics. Neurosurgery 2001, 49:614-9; discussion 619-21. Conclusion: Clot resolution can be accurately measured with simple CT scan results. These measures are highly reproducible. They demonstrate that human clot resolution can be described as a first order process.

Naff NJ, Carhuapoma JR, Williams MA, Bhardwaj A, Ulatowski JA, **Bederson J**, Bullock R, Schmutzhard E, Pfausler B, **Keyl PM, Tuhrim S, Hanley DF**. Treatment of intraventricular hemorrhage with urokinase: effects on 30-Day survival. Stroke 2000:31:841-47. Conclusion: Mortality from IVH is markedly reduced in a two cohorts of patients treated with aggressive care including ICU

support, ICP management and UK mediated clot lysis. Actual 30-day mortality was significantly lower than disease severity factor predicted mortality. An apparent reduction from 68 % to 20% was found.

Carhuapoma JR, Wang PY, Beauchamp NJ, **Keyl PM, Hanley DF**, Barker PM. Diffusion-weighted MRI and proton MR spectroscopic imaging in the study of secondary neuronal injury after intracerebral hemorrhage. Stroke 2000, 31:726-32. Conclusion: MRI can be used to evaluate biochemical injury to brain tissue including quantifying the amount of edema provoked by the ICH.

Carhuapoma JR, Barker PB, **Hanley DF**, Wang P, Beauchamp NJ. Human Brain hemorrhage: quantification of perihematoma edema by use of diffusion –weighted MR imaging. Am J Neuroradiol 2002, 23:1322-1326. Conclusion: Perihematoma edema as quantitated by the ADC of water in human brain, has a direct relation to the volume of blood clot in the tissue. A dose--injury relationship appears to characterize the volume of blood in brain tissue and the edema produced.

Naff NJ, **Keyl PM, Tuhrim S, Kraut M, Bederson J, Bullock RM**, Mayer S, Schmutzhard E, **Hanley DF**. Intraventricular Thrombolysis Speeds Blood Clot Resolution: results of a Randomized double-Blinded Controlled Trial. Neurosurgery 2003, 54(3):577-83; discussion 583-4. Conclusion: Randomization to the UK treatment arm and female gender favorably affected the clot resolution rate. In this controlled (but small) group of humans, UK was safely administered every 12 hours for six days. Mortality in the treated group was 0%, No symptomatic rebleeding occurred.

Ziai WC, Torbey M, Naff NJ, Williams MA, **Bullock R, Marmarou A, Tuhrim S,** Schmutzhard E, Pfausler B, **Hanley DF**, Frequency of sustained intracranial pressure elevation during treatment of severe intraventricular hemorrhage. Cerebrovascular Diseases. 2009, 27(4):411-2. Conclusion: ICP elevation is infrequently in IVH patients independent of thrombolytic treatment.

Qureshi AI, **Tuhrim S, Broderick JP,** Batjer HH, Hondo H, **Hanley DF.** Spontaneous intracerebral hemorrhage. NEJM 2001, 344:1450-1460. Conclusion: No established primary interventions for ICH or IVH exist.

Lapointe, M, Haines, S. Fibrinolytic therapy for intraventricular hemorrhage in adults (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2002. Oxford: Update Software. Conclusion: A controlled study is needed.

Naff N, Hanley DF. Low-dose rt-PA enhances clot resolution in brain hemorrhage. Submitted. Conclusion: rt-PA removes clot faster. Faster clot removal lead to earlier recovery of GCS. rt-PA is safe compared to controls.

Carhuapoma JR, Barrett RJ, **Keyl PM, Hanley DF, Johnson RR.** Stereotactic aspiration-thrombolysis of intracerebral hemorrhage and its impact on perihematoma brain edema. Neurocrit Care. 2008, 8(3):322-9. Conclusion: Perihematomal edema decreases sequentially as clot volume is removed.

Qureshi AI, Mendelow DA, **Hanley DF**. Intracerebral Hemorrhage. The Lancet. In Press. Conclusion: This review summarizes pathophysiological and clinical studies, and randomized trials over the past 5 years in primary and secondary ICH.

Hanley DF. Topical Review: Intraventricular hemorrhage: severity factor and treatment target in spontaneous intracerebral hemorrhage. Stroke. 2009, 40(4):1533-8. Conclusion: Small proof of concept studies, meta-analyses and preliminary pharmacokinetic studies support a positive shift in morbidity and mortality, if the IVH severity factor is properly addressed.

11.4. TRIAL DESIGN

This study is a double-blinded, multicenter, international, randomized study comparing the use of EVD combined with rt-PA to EVD combined with normal saline for the treatment of intraventricular hemorrhage.

The study is proposed to require 5 to 6 years of enrollment. All subjects will be followed through day 7, cessation of IVC, and at 1, 3, 6, 9, and 12 months, regardless of treatment assignment. Subjects will receive up to 12 test article administrations and will be required to attend follow-up clinic visits at 1, 6, and 12 months after onset of IVH. A telephone follow-up will occur, to assess functional outcome and quality of life, at 3 and 9 months.

11.4.1. SCREENING AND ELIGIBILITY CRITERIA

Inclusion Criteria

1. Age 18-80.
2. Symptom onset less than 24 hrs prior to diagnostic CT scan.
3. Spontaneous ICH ≤ 30 cc and IVH obstructing 3rd and/or 4th ventricles.
4. ICH clot stability: ICH must be ≤ 30 cc on initial presentation and not exceed 35 cc on subsequent pre-randomization stability scans. A CT scan performed 6 hours or more after IVC placement must be stable (difference is ≤ 5 cc) compared to the most previous CT scan as determined by the (AxBxC)/2 method.
   Temporary Criterion: If the clot is not stable (i.e., difference is > 5 cc), a repeat CT scan must be performed at least 12 hours later and compared to the most previous CT scan. Investigator may continue to screen every 12 hours up to 72 hours for the initial bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan and the clot remains ≤ 35 cc. If the size stabilizes (i.e., enlargement ≤ 5 cc between 2 sequential CT scans) and remains ≤ 35 cc, the patient is eligible.
5. IVH clot stability: The width of the lateral ventricle most compromised by blood clot must not increase by > 2 mm, allowing for movement of blood under influence of gravity.
   Temporary Criterion: If the clot is not stable (i.e., difference is > 2 mm), a repeat CT scan must be performed at least 12 hours later and compared to the most previous CT scan. Investigator may continue to screen up to 72 hours for the initial bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan. If the size stabilizes (i.e., enlargement ≤ 2mm between 2 sequential CT scans), the patient is eligible.
6. Catheter tract bleeding must be less than or equal to 5 cc on CT scan for stability.

Temporary criterion: If a catheter tract hemorrhage is present on the CT scan done 6 hours after IVC placement and is > 5 cc or > 5 mm, obtain a repeat CT scan 12 hours later. This includes any bleeding at the entry site or along the catheter tract that is 5 mm in diameter seen on any CT slice or is 5 mL on more than one CT slice. If the catheter tract hemorrhage further enlarges by > 5 cc or > 5 mm as compared to the most previous CT scan, the investigator may continue to screen by repeat CT scan every 12 hours for the bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan. If the size stabilizes (i.e., enlargement ≤ 5 cc or ≤ 5 mm between 2 sequential CT scans), the patient is eligible.

7. On stability CT scan, the 3rd and/or 4th ventricles are occluded with blood.
8. All patients randomized will have had EVD placed, ideally using no more than 2 complete passes (including "soft passes" using the original trajectory), on an emergent basis as defined by the "standard of care" neurosurgical/critical care decisions of the managing physicians. If more than 2 passes are required for placement, additional stabilization of IVC site will be determined with a CT performed at 24 hours after IVC placement.

   Temporary criterion: If no IVC is in place at the time the patient is initially screened, the decision to place an IVC may occur after the patient is initially screened but an IVC must be in-place and stable at the time of randomization.
9. Patients with primary IVH are eligible (i.e. with ICH=0).
10. SBP < 200 mmHg sustained for the 6 h before drug administration (closest to randomization).

    Temporary criterion: Blood pressure inclusion criteria not met when the patient is screened: Most vital signs are stabilized within the time window for enrollment.
11. No test article may be administered until at least 12 hours after symptom onset.
12. Able to randomize within 72 h of CT scan diagnosing IVH (provided the time of symptom onset to diagnostic CT does not exceed 24 h).

    Temporary criterion: The 72 hour limit may be extended with approval from the Coordinating Center to allow for clot stability (ICH, IVH, catheter tract), INR stability, or other valild reason.
13. Historical Rankin of 0 or 1.

Exclusion Criteria

1. Suspected (unless ruled out by angiogram or MRA/MRI) or untreated ruptured cerebral aneurysm, ruptured intracranial AVM, or tumor. Treatment of an existing aneurysm or AVM must have occurred at least 3 months before the current onset.

   Temporary criterion: This is especially important in primary IVH, when no ICH source is found. CT angiogram, angiogram, MRA/MRI, or general diagnostic study (prior to confirming patient eligibility in the protocol) is standard of care to rule out underlying etiology. If the CT angiogram, angiogram or MRA/MRI is negative, the patient is eligible. The PI must document rationale if imaging is not done.
2. Presence of a choroid plexus vascular malformation or Moyamoya disease.

3. Clotting disorders. Subjects requiring long-term anti-coagulation are excluded.
   Temporary criterion: Reversing anticoagulation will be permitted where long-term anticoagulation is not required.
4. Use of Dabigatran, Apixaban, and/or Rivaroxaban (or a medication from the same medication class) prior to symptom onset.
5. Platelet count < 100,000, INR > 1.4.
   Temporary criterion: Low platelet counts etc. on admission can normalize within 24 hours as can an INR normalize to $\leq$ 1.4.
6. Pregnancy (positive serum or urine pregnancy test).
7. Infratentorial hemorrhage
8. Thalamic bleeds with apparent midbrain extension with third nerve palsy or dilated and non-reactive pupils. Other (supranuclear) gaze abnormalities are not an exclusion. Note: Patients with a posterior fossa ICH or cerebellar hematomas are ineligible.
9. SAH at clinical presentation (an angiogram (angiogram, CTA, MRA/MRI) must be obtained when the diagnostic CT scan shows SAH or any hematoma location or appearance not strongly associated with hypertension. If the angiogram or other imaging does not detect a bleeding source to account for the hemorrhage, the patient is eligible for the study.) Subsequent appearance of cortical SAH secondary to clot lysis is not a dosing endpoint.
   Temporary criterion: An angiogram must be obtained when the diagnostic CT scan demonstrates subarachnoid hemorrhage or any hematoma location suggestive of aneurysm or appearing not strongly associated with hypertension. If the angiogram/imaging does not demonstrate a bleeding source that accounts for the hemorrhage, the patient is eligible for the study.
10. ICH/IVH enlargement that cannot be stabilized in the treatment time window.
    Temporary criterion: ICH enlargement during the 6-hour stabilization period (6 hours after IVC placement): It is permitted to screen up to 72 hours after diagnostic scan. If the ICH clot size stabilizes (i.e., enlarges no more than 5 cc) and does not exceed 35 cc (an ICH clot size of 35 cc allows for stabilization of a 5cc expansion for those patients at the upper limit of the ICH clot size limit), the patient is eligible.
11. Ongoing internal bleeding, involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts. (Patient with prior bleeding that is clinically stable for 12 h or more without any coagulopathy or bleeding disorder is eligible).
12. Multi-focal, superficial bleeding, observed at multiple vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or site of recent surgical intervention.
13. Prior enrollment in the study.
14. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated. Subjects who are not expected to survive to the day 180 visit due to co-morbidities and/or are DNR/DNI status prior to randomization are excluded.
    Temporary criterion: Although these situations are often irreversible, under other conditions, change can occur over 24 hours.
15. Planned or simultaneous participation (between screening and Day-30) in another interventional medical investigation or clinical trial. Patients involved in observational, natural history, and/or epidemiological studies not involving an intervention are eligible.

16. No subject or legal representative to give written informed consent.

11.4.2. STUDY ENROLLMENT PROCEDURES

Identifying and recruiting patients. Study Population. Approximately 75 study centers throughout the US, Canada, and Europe will screen and identify 500 subjects with intraventricular hemorrhage secondary to supratentorial ICH or primary IVH, and without suspected underlying structural etiology (tumor, vascular malformation or aneurysm). Patients will be identified and recruited through site emergency departments, clinical stroke services, and direct admissions to the neurological ICUs. Eligible patients will be recruited from all acute hemorrhagic stroke subjects who are diagnosed with intraventricular hemorrhage by CT scan within 24 hours of symptom onset. Periodic monitoring of gender and ethnicity specific rates of recruitment will be carried out and recruitment criteria will be adjusted if necessary to ensure that women and minorities comprise a proportionate fraction of the study population compared to the general population.

Consent procedures. Informed consent must be obtained from the patient, or if the patient is aphasic, confused, or obtunded, the legal representative of that patient. Patients will not be treated if consent cannot be obtained from a competent patient or from his/her legal representative.

Randomization. After determination that dosing can be initiated within the 72 hours after diagnostic CT scan, the patient meets all eligibility criteria, and informed consent has been obtained from the patient or legal representative, eligible patients will be randomized to either the EVD + rt-PA group or the EVD + placebo group via the VISION EDC system (software provided by Prelude Dynamics Inc., Austin, Texas; study-specific implementation design developed by Emissary International LLC, Austin, Texas). Patients randomized to either group must have had an EVD placed per standard of care prior to randomization.

Study Entrance. Patients presenting with intraventricular hemorrhage requiring the placement of an EVD per standard of care will be eligible for randomization. The study coordinator will screen patients for all inclusion and exclusion criteria. The risks and benefits of rt-PA or normal saline irrigation of the external ventricular drain will be explained to all eligible candidates by the principal surgeon, the principal neurologist or by a consent designee at each center. All patients agreeing to the study will be consented and randomized.

Tracking Procedure. All study center investigators and study coordinators must have an established relationship with their emergency department personnel and must be routinely notified of hemorrhagic and ischemic strokes. Each center will design a system for patient tracking that best suits its needs according to time, personnel, and the patient population. The study coordinator will be responsible for tracking subjects and scheduling appointments. The study coordinator will inform subjects of the follow-up expectations when informed consent is obtained, and will maintain contact through telephone calls and letters. The Coordinating Center database will drive a monthly report and centers will receive emails listing subjects due for assessment and overdue for assessments. The study coordinator will be required to document in the VISION EDC system whenever subjects are lost to follow-up or assessments are overdue. A subject is only considered “lost to follow-up” if contact is not achieved at the day 365 visit. Attempts to find and establish contact with a subject must be made at every follow-up time-point, even

if unsuccessful at an earlier time-point. A subject lost to follow-up will not be tolerated; in such case the site investigator will be placed on a remediation plan to improve subject tracking.

Facilities. To be eligible as a site, a center must be able to demonstrate uniform referral, triage, and medical management practices. Each center must have emergency stroke transport services, stroke triage screening, a full time neurovascular neurosurgeon, and (a) stroke research coordinator(s). To assure standardization of technical capabilities, the study chairman and appropriate coordinating center administrators will review each site's triage capabilities, emergency department facilities, pharmacies, imaging resources, and neurological ICUs. The Executive Committee along with approval from NINDS is ultimately responsible for the selection of the sites and investigators.

Documentation for ineligibility. Monthly reports of subject accrual (screened but not enrolled and enrolled) and other protocol compliance data will be provided by the coordinating center. All subjects with intraventricular hemorrhage, whether eligible or not, who have been screened by study personnel at participating hospitals within 72 hours of diagnostic CT will be documented in the VISION EDC system. Reasons for exclusion for each patient not entered into the trial will be recorded. Each participating hospital will enter screening data into the VISION EDC system once a month for review of screening and eligibility performance. The EDC system is designed as an interactive tool to assist the site coordinator in the screening process by prompting for all permanent inclusion/exclusion criteria first. If the subject passes this section of the screening process, the coordinator is then prompted to screen for all temporary inclusion/exclusion criteria with appropriate time windows noted for each. Once all fields are completed, or an inclusion/exclusion criterion is failed, the system will either document the subject as a screen failure or prompt the coordinator to randomize the eligible subject.

Study centers failing to enroll within the six-month start-up period will be undergo remediation with possible termination. Study centers in this situation may appeal to the coordinating center. If the study center can present a strong case for extenuating circumstances, then termination may be waived and the site will remain in the trial for one additional 6-month period with the same enrollment expectation.

11.5. Study Interventions

11.5.1. Interventions, Administration, and Duration

Either 1.0 mg/1 mL of rt-PA or 1 mL of normal saline will be administered via the EVD. This will be performed via isovolumetric injection into the ventricle with up to a 4.0 ml flush of sterile saline to ensure clearance of the study drug from the catheter and delivery to the clot. Injection will be followed by closure of the catheter for 1 hour and then opening of the EVD for drainage of clot and CSF until the next injection every 8 hours. The treatment will continue for up to 12 doses of drug.

Dual catheters. Where dual catheters are utilized doses are to be alternated every eight hours. Dosing via the catheter contralateral to the clot will be discontinued when the 3rd and 4th ventricles are open. Dosing of the ipsilesional ventricle may continue if a second catheter is located in or near the residual blood. Dosing via this catheter may continue until one of the following occurs: 1) an estimated 80% of intraventricular clot has been removed, 2) IVH related mass effect (dilated or shifted ventricle) has resolved, or 3) a total of 12 doses have been administered. If the catheter cannot remain patent, saline irrigation may be performed if clogging occurs. No other irrigating agents may be used. Irrigation

events are to be recorded on the eCRF. Replacement of dual catheters will be guided by neurosurgical clinical judgment. The Neurosurgical Center will review all catheter placements.

Supportive care will include ICP management with CSF drainage as well as osmotic therapy, hyperventilation, analgesic-sedation, and where indicated to control ICP, induced coma and surgical management. These modalities are well described in the AANS head injury guidelines and can be found on the trial website: www.cleariii.com. The extent and temporal pattern of supportive care will be documented systematically as the treatment intensity level (TIL) every four hours. ICP medications will be administered to maintain a goal of ICP less than 30 mm Hg and CPP greater than 70 mm Hg. These medications will be administered in compliance with the AANS head injury guidelines (American Association of NS. Guidelines for the management of severe head injury. Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. J Neurotrauma 1996;13(11):641-734.).

11.5.2. Handling of Study Interventions

Alteplase (rt-PA) is a sterile, white to pale yellow, preservative-free lyophilized powder intended for intravenous administration after reconstitution with sterile water for injection, USP. It is important that Alteplase be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. All injections should be prepared in compliance with USP 797 guidelines (Immediate-use CSP). The reconstituted preparation results in a colorless to pale yellow transparent solution containing Alteplase 1.0 mg/ml at approximately pH 7.3. The rt-PA or normal saline will be prepared in a syringe that will be delivered to the ICU along with a 4 ml flush in a separate packet.

For further details, see the Alteplase Package Insert and Chapter 12 of the Manual of Operations and Procedures.

Normal saline will be used from local pharmacy stock. Preparation of the placebo will be the same as that of the rt-PA as outlined in Chapter 12 of the Manual of Operations and Procedures so as to maintain blinding of the study drug. Accountability forms will be provided to the site to document the preparation and dispensing of normal saline.

Drug accountability forms will be provided to the site to document how many vials of rt-PA were received and how many were used over the course of the study. The time each vial's contents are prepared will be noted on the source documentation.

To maintain blinding, drug accountability will not be checked during monitoring visits to maintain blinding. The study site will keep a record of all rt-PA dispensed and administered to the subjects. This record will be reviewed by the Study Pharmacist on an annual basis, or sooner for high enrolling sites. All unused study medication may be discarded on site according to each center's specific policy for disposal of pharmaceutical waste. Prior to disposal of the drug, the Central Study Pharmacist must receive a copy of the center's policy for study drug disposal (pharmaceutical waste) and documentation of the drug to be discarded. The total amount of study drug administered will be recorded on the source documents and case report forms.

11.5.3. Concomitant Interventions

Required Interventions. All subjects randomized will receive up to 12 doses of study drug. Any subjects who are randomized and receive the first dose of study drug will be followed and analyzed as intent to treat.

Permitted Interventions: Study center standard of care policies may govern the use of low molecular weight, fractionated and unfractionated heparins for DVT prophylaxis during the acute treatment and follow-up periods. Heparin flushes of systemic lines are also permitted. Use of enoxaparin for DVT prophylaxis in the ICU at the usual doses of 30 mg SC or 40 mg SC QD is permitted as long as the patient has good renal function (creatinine clearance of > 30 ml/min) or does not have an unusually low body weight (< 45 kg).

Prohibited Interventions. Use of antithrombotic or antiplatelet agents such as Coumadin (warfarin) and Dabigatran, Apixaban, Rivaroxaban, glycoprotein IIb/IIIa inhibitors (eptifibatide/Integrilin, abciximab/Reopro, tirofiban/Aggrastat), ASA, clopidogrel/Plavix is prohibited prior to the day 30 visit. These agents may be administered after day 30.

The use of urokinase, tenecteplase, retevase, desmoteplase, or any other thrombolytic agent administered via the IVC is prohibited. Clogged catheters should be treated with normal saline flushes.

Precautionary Interventions. If the intraventricular catheter needs to be replaced or repositioned, or if a second catheter is placed during dosing, wait 24 h after the most recent dose to perform the procedure. A stability CT scan must then be done $\geq$ 6 h after all placements/repositioning to confirm correct placement, clot stability, and absence of significant blood along the catheter tract. Once these are confirmed by the site and Neurosurgical Center, dosing may restart.

If a subject experiences asymptomatic bleeding (ICH expansion $\leq$ 5 cc, IVH expansion as assessed by $\leq$ 2 mm increase in 2 out of 3 ventricular regions, or catheter tract hemorrhage that is $\leq$ 5 mm in the largest diameter), continue the dosing and CT schedule. If the bleeding is larger than these thresholds, with or without mass effect, the next scheduled dose is skipped and a repeat CT scan is done $\geq$ 24 h after the previous dose. If the ICH, IVH, and catheter tract hemorrhage are stable (i.e., has not further grown by > 5 mm), then dosing may restart. (See Appendix 2: Catheter Tract Screening Decision Algorithm).

Particular caution needs to be observed with renal dialysis patients receiving rt-PA. Because this group of patients can experience wide variations in blood pressure with dialysis attendant cardiac volume changes, attention to long term and intra procedure blood pressure control is important. Similarly, attention to regional anti-coagulation management is important.

11.5.4. Adherence Assessment

Protocol adherence will be determined by review of data recorded on the case report forms that has been verified through comparison with the medical record and other source documentation. Compliance and treatment fidelity will be reported overall and by center to the DSMB at each scheduled review session. Study centers demonstrating poor protocol compliance will be retrained and, if necessary, replaced.

[Protocol continues on next page.]

11.6. Clinical and Laboratory Evaluations

11.6.1. Schedule of Evaluations

	Screening	Pre-Randomization (Baseline)	Randomization (Day 1)	Days 1-7	IVC Removal	Day 30 (+/- 7 days)	Day 90 (+/-7 days)	Day 180 (+/-14 days)	Day 270 (+/- 14 days)	Day 365 (+/- 14 days)
Informed Consent		X								
Diagnostic CT (SOC)	X									
Diagnostic CTA or routine angiogram (SOC; not required in Germany)	X									
IVC Placement (SOC)	X									
Stability CT (SOC)	X									
Neurosurgical Center review of IVC		X		X	X					
Blood pressure (over 6 hours)		X								
Medical/Treatment History	X									
Pregnancy Testing	X									
Toxicology Screen	X									
Dosing Q8Hr +/-2 hrs				Up to 12 doses	Open to drain for 24 hr post last dose					
CT Scan				Days 1-5 & 1 & 3 days post last dose		X				X
Vital Signs Q4Hr +/- 1hr				X	Daily for EVD management only	BP only		BP only		BP only
Lab Assessments	X	X		X						
AE/SAE capture			Starting point for recording AE/SAEs	X	Neurological AEs, all SAEs, and all Medical Events of Interest only					
NIHSS		X (capture if done SOC)	X	Day 7		X		X		X
Barthel Index	X (Historical)					X	X	X	X	X
Modified Rankin	X (Historical)					X	X	X	X	X
GOSE						X		X		X
Stroke Impact Scale						X		X		X
Mini-Mental Exam						X		X		X
EQ-5D						X	X	X	X	X
PBSI						X		X		X
Personal Health Utility AssessmentInterview								X		

†Certified examiners must complete the 1, 3, 6, 9, and 12 month follow-up visits.

11.6.2. Timing of Evaluations

Pre-Randomization Evaluations

Screening
Screening assessments can take place any time after the subject has been diagnosed with an IVH up to 72 hours after the time of the CT scan diagnosing the IVH.

Pre-Randomization
Pre-Randomization evaluations should be done during the screening period but must be completed prior to randomization.

Randomization (Day 1)
Randomization should occur as close as possible to the time that all eligibility criteria are met. If randomization is postponed to accommodate scheduling (i.e., it is preferable to wait until 6 am to randomize instead of midnight), a CT scan should be repeated to confirm stability of the ICH, IVH, and catheter tract and blood pressure stability should be confirmed prior to giving the first dose. The first dose of study drug should be administered as close to randomization as possible.

On-Study Evaluations. The acute phase of the protocol is defined as day 1 (date of randomization) through day 7. All subjects will receive intraventricular injections of study drug starting on Day 1 and ending on Day 4, or earlier if an endpoint is satisfied. The follow-up phase of the protocol begins on Day 8 and continues through the 12-month follow-up visit.

Intervention Discontinuation Evaluations. Monitoring of vital signs includes blood pressure, GCS, neuroworsening, temperature, etc. every four hours through day 7. (See 6.3.11: Vital signs.) Beginning with day 8 and ending with the removal of the last IVC placed, a once daily assessment of ICP, total CSF drainage, and drip chamber height will be collected retrospectively at the 30 day follow-up visit or sooner. We will record and analyze all CT scans ordered as standard of care.

The definition of bacterial ventriculitis is as follows: Culture speciation of an organism within a CSF sample from the ventricular drain in association with 1) fever AND elevated peripheral white blood cell count, OR in association with 2) greater than 25% rise in cerebral spinal fluid white blood cell count as compared to the most previous sample. Both serum and CSF white blood cell counts are performed daily as part of the protocol.

Non-bacterial or chemical ventriculitis is assigned to all episodes of infection meeting the definition of bacterial ventriculitis except there is no positive CSF cultures or other independent proof of bacterial infection.

All infections, with and without positive CSF cultures, will be reported to the safety and monitoring committee so that an independent assessment of clinical significance may be made as necessary.

We consider both bacterial ventriculitis and bacterial meningitis serious adverse events and treat both the same. This is the most conservative safety profile. We provide separate SAE codes for a clinical

determination between ventriculitis and meningitis and bacterial and non-bacterial, to accommodate investigator diagnostic classifications.

Subjects withdrawn early from treatment or who withdraw consent or are lost to follow-up will not be replaced. If a subject is withdrawn early from treatment due to a clinical safety endpoint, we expect standard clinical judgment to be applied to continue to monitor the subject until resolution of the event including but not limited to repeat CT scans and repeat laboratory assessments.

Subjects withdrawn early from the treatment protocol are asked to return to clinic for all scheduled follow-up assessments including the one, three (telephone contact), six, nine (telephone contact) and 12 month visits.

Discontinuation of Drug Administration. Test article injections will continue as defined by the protocol, unless EVD is discontinued, an endpoint of clot lysis is reached (i.e., both 3rd and 4th ventricles are open, IVH related mass effect [dilated or shifted ventricle] is treated, estimated 80% resolution of the IVH clot), or an adverse treatment endpoint occurs, such as symptomatic hemorrhage. IVH clot resolution of 80% will be estimated by comparing the daily dosing CT scan Graeb score with the Graeb score assigned to the stability CT scan used for randomization.

If, after dosing is discontinued based on 3rd and 4th ventricle clearing, blood redistributes and the 3rd or 4th obstruct again, then dosing may be resumed, provided no more than 12 doses are given and rebleeding is ruled out.

A CT scan must be done 1 and 3 days after the last dose is administered (approximately 24 and 72 h post last dose respectively) to monitor for new bleeding or bleeding extension. After last dose the EVD will be closed for one hour and then reopened to drain for 24 hours to allow for complete removal of test article. Subsequently, EVD will be discontinued when the patient tolerates 24 h of IVC closure with no sustained elevation of ICP above 15 mmHg using the protocol below.

Patient care standards require the restoration of adequate, spontaneous CSF circulation before removal of the drain. Thus opening the 3rd and 4th ventricles and removal of blockade of the lateral ventricles causing mass effect must be addressed prior to EVD removal. CSF resorptive capacity must be gauged according to CSF drainage rate. Adjusting the height of the drainage system drip chamber controls the rate of external CSF drainage, and hence the ICP that must be exceeded before the drainage occurs. The drip chamber is usually raised in 5-mmHg steps every 12 to 24 hours. As this is done, the CSF circulatory pathways and resorptive mechanisms are gradually challenged. If CSF circulation and resorption are insufficient, most of the CSF will continue to drain through the IVC, but if CSF resorption is sufficient, little CSF will drain externally. CSF resorption is usually considered inadequate if more than 200 to 250 cc CSF per day drains through the IVC with the drip chamber set at 15 mm Hg. When less than 100 cc of CSF drains per day, CSF drainage should be stopped and ICP should be monitored for 24 hours as final confirmation that spontaneous CSF resorption is adequate and ICP will not rise to dangerous levels. If ICP stays in an acceptable range, and there is no neurological deterioration, the IVC can be removed. If ICP increases in a sustained manner above 30 mm Hg, or there is neurological deterioration, the IVC should be reopened for further drainage or shunt surgery can be elected. The duration of EVD will be considered as the time between the initial placement of the IVC and the time

that the last IVC was discontinued. Cerebral spinal fluid drainage volume and ICP values will be monitored and assessed daily to evaluate compliance with the EVD maintenance and discontinuation protocols. This criterion is a specific and widely-accepted clinical standard that has been uniformly applied in the prior IVH trials. This criterion will be applied to both randomized groups of subjects.

While the goal of the interventional therapy is the restoration of normal CSF flow, the study group recognizes that the resolution of intraventricular clot as determined by CT is an endpoint for test article administration. EVD drainage cessation and ICP challenge should be performed if the third and fourth ventricles are open (no obstructing blood in the third and fourth ventricles and CSF seen clearly within the ventricular space). Thus, test article administration will not continue if the IVC is required for management of ICP after resolution of blood clot. Similarly, additional ICH or IVH bleeding, a disseminated systemic bleeding event, or in the opinion of the investigator any test article-associated event will be considered an endpoint for test article administration. Test article administrations will be terminated before the next scheduled dosing time point, if clot resolution is achieved. Test article administrations will be terminated after 12 doses of test article have been given.

Post-Intervention Evaluations. The follow-up phase of the protocol begins on day 8 and continues through the 12-month follow-up visit. All subjects will be required to return for a follow-up clinic visit at months 1, 6, and 12, with a CT scan to be done at the 1 and 12 month visit. A telephone follow-up visit will occur at months 3 and 9. Daily monitoring of all adverse events will continue until day 7. This includes monitoring of additional medications used, additional procedures and ICU care required. Serious adverse events will be monitored throughout the initial hospitalization. Serious adverse events, neurological adverse events, VP shunt placement, and total time at home (i.e., excluding hospital re-admissions and admission to rehabilitation facilities) will be recorded at all subsequent follow-up visits.

Final Evaluations. At the subject's final visit to occur at approximately 12 months post ictus, the following will be done: CT scan, NIHSS, Barthel Index, video-taped modified Rankin Scale, extended GOS, Stroke Impact Scale, Mini-Mental State Exam, EQ-5D, and PBSI. Also at this time the subject will be asked about any new neurological adverse events or any serious adverse events that may have occurred since the nine-month telephone contact. The subject will also be specifically asked about any neurosurgical procedures, hydrocephalus, and shunting. All serious and non-serious adverse events that occurred prior to the 12 month visit but remain documented as "ongoing" will be confirmed as "ongoing" or documented as "resolved" and a resolution date recorded. The examiner will document if the subject was prescribed and is compliant with any blood pressure medications at the 12 month visit and document if any of the following have occurred since the nine-month telephone contact: death, new bleeding on CT, bleeding extension on CT, ventriculitis, permanent shunt placement, and/or lumbar drains/punctures (after EVD removal). The subject will be instructed that this is the final visit.

Pregnancy. Women who become pregnant during the follow-up period will be followed through the 12 month visit to document clinical and functional outcome but no CT scans will be done.

11.6.3. Special Instructions and Definitions of Evaluations

Informed Consent. Consent forms must be reviewed by the Coordinating Center for completeness and accuracy prior to submission to local study center IRB/Ethics Committees. This review must occur after each time the document is modified.

The informed consent process can begin at any time between EVD placement and randomization, but must be obtained prior to randomization. A signature on the consent form does not translate into enrollment in the study. Only after all inclusion/exclusion criteria have been met and informed consent has been signed can a patient be randomized into the study.

Informed consent must be obtained from the patient, or if the patient is aphasic, confused, or obtunded, the legal representative of that patient. Patients will not be treated if consent cannot be obtained from a competent patient or from their legal representative.

The study center will document signed consent in a written progress note, by placing a signed copy in the hospital medical chart and keeping the signed original in the study subject file. A signed copy should be given to the subject as well. The study monitor will review and confirm signed consents while reviewing subject data collection forms.

Blinding. This is a double-blind investigation. The subject, investigators, coordinators, medical care team, Coordinating Center personnel, and the Study Leadership are all blinded to treatment assignment. If unblinding occurs accidentally, the Coordinating Center must be notified in writing immediately by completing a form in the VISION EDC within 24 hours of the event. The subject may continue on protocol and decisions to include the subject's data in primary analyses will be made depending on the circumstances of the unblinding event. If the subject experiences a life-threatening event and the investigator feels it is necessary to know the treatment assignment in order to medically treat the subject, the investigator must contact the Study Chairman. The Study Chairman will consult with the Medical Safety Monitor to determine if unblinding is necessary. Efforts will be made to maintain blinding at all levels (local, central, etc) to ensure data integrity. Blinding of study center personnel will be queried and documented at each follow-up visit.

Diagnostic CT (Standard of Care). This CT scan is the initial CT used to diagnose the IVH and is done per standard medical care upon presentation to the Emergency Department. If this scan is done at an outside hospital prior to transfer to the enrolling center, the outside hospital scan must be obtained and uploaded to the EDC. CT angiogram or routine angiogram with evaluation for "spot sign" is encouraged and considered standard of care to complete the evaluation for aneurysm, AVM, or other malformations. If this imaging is not done, the rationale must be documented in the EDC system. The diagnostic CT scan will be used to calculate the ICH and estimate the IVH size and as the start time for the 72 hour enrollment window. ICH size greater than 30 cc on this scan will exclude the patient from participation. The Diagnostic CT scan will be compared with the first Stability CT scan to determine if the hemorrhage continues to expand or if stability has been achieved (ICH size within 5 cc [upper limit of 35 cc], the width of the IVH clot in the lateral ventricle most compromised by blood clot within 2 mm, catheter tract $\leq$ 5 mm). A copy of the Diagnostic CT electronic image will be uploaded to the EDC prior to randomization. The Reading Center will centrally review this scan to confirm eligibility and to measure ICH, IVH, and catheter tract clot volume/stability.

At each study center ICH volume will be determined in a standardized manner. Instructions for calculating ICH volume are included in Chapter 18 of the Manual of Operations and Procedures.

IVH size will be determined by measuring the width of ventricular clot in the lateral ventricle most compromised by blood, excluding any CSF that accumulates for obstruction, at 3 locations along the ventricle long axis using a ruler (or calipers) on CT scan. Stability of the IVH is defined as no more than a 2mm increase in any 2 of the 3 cross-axis measurements.

The size of the ICH and the IVH along with the date and time of the diagnostic CT scan should be documented in the medical record as source documentation.

IVC Placement. Eligible patients will be identified upon presentation, diagnosis of IVH, and IVC placement. The placement of the intraventricular catheter is done per standard medical care prior to randomization into the study. The IVC must be placed ideally using one or two complete passes, which includes "soft passes" using the original trajectory. If more than 2 passes are required for placement, additional stabilization of IVC site will be determined with a CT performed at 24 hours after IVC placement. Consideration of EVD placement goals in light of current safety data may be helpful. The ventricular catheter tip is placed in an appropriate location within the ventricular system. The catheter should not irrigate tissue or the subarachnoid space. No drug will be administered if the catheter does not access the intraventricular clot via the ventricular CSF space. Elective repositioning (pullback) and emergency replacement of any EVD as clinically indicated is permitted prior to dosing.

The date and time of placement of the IVC, the size of the catheter used, and the first recorded ICP from the monitor should be documented in the medical record as source documentation.

Neurosurgical Center Review. All subjects, regardless of treatment assignment will be evaluated for adequacy of EVD placement by the Surgical Center prior to randomization and will continue through the end of the acute treatment period (72 h post last dose). The surgical training program (a self-instruction, narrated Microsoft PowerPoint presentation), which is part of the surgical protocol (MOP Chapter 17.0: Surgical Center) specifically articulates criteria for placement of a second EVD (clot producing trapped ventricles, clinically important shifts, or panventricular enlargement with effacement/ischemia-- typically with larger IVH > 40 cc), or for elective catheter repositioning or replacement (infection, obstruction, malposition, unplanned migration or withdrawal of previous EVD), with required stability before starting or resuming instillation of drug or placebo. Criteria for instillation of drug or placebo in cases where more than one EVD is in place are also clearly articulated in the surgical protocol. Each site's surgeon-investigator will review and approve the use of the EVD insertion protocol to insure a uniform approach to this element of clinical care.

The Neurosurgical Center personnel will review the radiological images for each subject prior to randomization and after every catheter placement and repositioning. Personnel will document the results of their review in a separate section of the EDC not viewable by sites. The EDC will notify the site and share with the site personnel a summary report of the Neurosurgical Center review instructing the site to reposition the catheter, add a second catheter, or that the catheter placement was adequate and the site may proceed with randomization or continue dosing.

Stability CT (Standard of Care). The Stability CT scan must be done at least 6 hours after placement of the initial IVC and at least 12 hours after any subsequent IVC placements prior to dosing. This scan is normally done per standard medical care to confirm correct placement of the IVC in the ventricular system. If this CT is not done per standard medical care at a participating study center, informed consent must be obtained prior to ordering the CT. Catheter adjustments will be made at this time if necessary. All CT scans done after the Diagnostic CT and prior to randomization are considered stability CT scans. All stability CT scans must be reviewed by a radiologist or an investigator and compared to the Diagnostic or most previous CT to confirm that the ICH and IVH clots are stable and that there is no bleeding in the catheter tract. If catheter tract bleeding is documented on this scan and is $\leq$5 mm the patient remains eligible for randomization (Appendix 2). Clot stability is defined as no enlargement greater than 5 cc between two scans. If any clot has enlarged greater than 5 cc, the patient must be rescanned 12 hours later prior to start of study drug and 24 hours later during active dosing. A comparison must then be made with the previous scan to ensure clot stability. A copy of all CT scans done after the Diagnostic CT and prior to randomization will be uploaded to the EDC prior to randomization. The Reading Center will centrally review this scan/these scans to confirm eligibility and to measure ICH, IVH, and catheter tract clot volume/stability.

The size of the ICH, IVH, and catheter tract hemorrhage along with the date and time of all stability CT scans should be documented in the medical record as source documentation.

Blood Pressure. The patient's blood pressure must be stable to be eligible for randomization. Blood pressure stability is defined as SBP < 200 mmHg for a period of 6 hours. This 6-hour period must be maintained and documented as close to but prior to randomization as possible. Aggressive blood pressure management to maintain SBP < 200 mmHg will be required throughout the first 7 days of the ICU stay to reduce the risk of bleeding events. Transition to long-acting, oral medication(s) should occur as soon as blood pressure control is achieved to: 1) initiate long-term control and 2) minimize the chance of rebound hypertension.

The systolic and diastolic pressures over the six-hour monitoring period should be documented in the medical record as source documentation.

Medical/Treatment History. The medical/treatment history must be documented as part of the screening process to rule out exclusion criteria (i.e., serious concurrent illness, clotting disorder, known risk for embolization, etc.). Medical history obtained for data collection purposes may be recorded in the medical record as source documentation and then transcribed to the VISION EDC or can be recorded directly on the eCRF to document discussions with the patient, family, and/or health care team not otherwise collected in the medical record.

Pregnancy Testing. Female patients of childbearing ability (i.e., of childbearing age and not surgically sterilized) must have a negative urine or serum pregnancy test to be eligible. If this test is not done per standard medical care at a participating study center, informed consent must be obtained prior to ordering the test.

The date and time of the pregnancy test and the result should be documented in the medical record as source documentation.

Toxicology Screen. The toxicology screen may or may not be done per standard medical care. A urine or blood toxicology screen is requested per protocol to document the presence of cocaine in the patient's system which may have contributed to the onset of the hemorrhagic stroke. This screen should be done as close to the time of presentation as possible so as to not capture as part of the screen substances given to the patient for treatment. If a toxicology screen is not done as part of standard medical care at a participating study center, the screen should be listed in the informed consent document and consent should be obtained prior to ordering the screen. The results of the toxicology screen are for data collection purposes only and do not have bearing on eligibility for the study.

The date and time of the toxicology screen and the results should be documented in the medical record as source documentation.

Dosing. Randomized subjects will receive isovolumetric injections of either 1.0 mg/1.0 mL of rt-PA or 1 mL of normal saline followed by up to 4.0 mL of flush via the intraventricular catheter every 8 hrs for up to 12 doses. There is a 2 hr window on either side of the 8 hr dosing schedule to allow for scheduling problems, stability determination, INR correction, or any other concern the PI may have regarding giving the dose on schedule. This schedule adjustment should be used as infrequently as possible to maintain a q8hr schedule for dosing consistency.

If a dose must be held or delayed to correct an INR lab value above 1.4, skip the next scheduled dose, institute corrective therapy, and re-assess the INR 12 hours later. If the INR remains > 1.4, continue corrective therapy as required or the investigator may discontinue dosing. Once the INR is corrected, dosing may be resumed.

Recommendations for INR corrective therapy (Morgenstern, et al. Stroke 2010;41:2108-29):

1. Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively (Class I; Level of Evidence: C). (New recommendation)
2. Patients with ICH whose INR is elevated due to oral anticoagulants (OACs) should have their warfarin withheld, receive therapy to replace vitamin K-dependent factors and correct the INR, and receive intravenous vitamin K (Class I; Level of Evidence: C). PCCs have not shown improved outcome compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP (Class IIa; Level of Evidence: B). rFVIIa does not replace all clotting factors, and although the INR may be lowered, clotting may not be restored in vivo; therefore, rFVIIa is not routinely recommended as a sole agent for OAC reversal in ICH (Class III; Level of Evidence: C). (Revised from the previous guideline)
3. Although rFVIIa can limit the extent of hematoma expansion in noncoagulopathic ICH patients, there is an increase in thromboembolic risk with rFVIIa and no clear benefit in unselected patients. Thus rFVIIa is not recommended in unselected patients. (Class III; Level of Evidence: A). (New recommendation)

4. The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is unclear and is considered investigational (Class IIb; Level of Evidence: B). (New recommendation)
5. Patients with ICH should have intermittent pneumatic compression for prevention of venous thrombembolism in addition to elastic stockings (Class I; Level of Evidence: B). (Unchanged from previous guideline)
6. After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset (Class IIb; Level of Evidence B). (Revised from the previous guideline)

In the event of severe or life-threatening anaphylaxis or hypersensitivity reaction, the treatment phase would be discontinued. The patient would not be retreated with test article. A description of the reaction would be added to the patient's medical record as a serious adverse event for future reference.

All manipulations of the system will be performed using sterile technique. There is a demonstrated low incidence of infection associated with this procedure. It will be up to each study center to use antibiotic coverage per standard of care for this type of procedure. An infectious disease consult is suggested for any patient if there are clinical signs of ventriculitis or meningitis. If an unexpected high rate of infection occurs over the course of enrollment, then the DSMB will make appropriate changes in aseptic regimen if necessary.

Before dosing, the investigator will be required to view the most recent CT scan, confirming that the catheter tip is placed in an appropriate location within the ventricular system. This requirement will control the delivery of test article into CSF spaces containing clot that can be lysed. In addition, an unscheduled CT scan is required should a subject clinically deteriorate or significantly improve his or her GCS score by greater than 2 points on the motor scale sustained over 8 hours, or sooner if clinically indicated. These additional safety provisions will keep under surveillance the most ideal time to stop test article administration.

Intracranial pressure, cerebral perfusion pressure, and blood pressure will be monitored before, during, and after each injection. After injection, the IVC will be closed for 1 hour to prevent drainage of the test article away from the clot and to allow adequate time for drug-clot interaction. The IVC will be reopened within that initial hour only if necessary to control medically refractory ICP elevation. Medically refractory ICP will be treated by a standardized regimen of hyperventilation, osmotic therapy, diuresis, and pharmacological sedation before opening the IVC prematurely. After 1 hour of closure, the IVC will be opened with an appropriate drainage gradient. ICP will be measured every 4 hours, or more frequently, as clinically indicated. A neurosurgical consult should be obtained for sustained intracranial hypertension. Sustained intracranial hypertension is defined as ICP greater than 20 mmHg for 2 or more consecutive hours despite maximal medical ICP management.

The first IVC injection will occur after randomization, no sooner than 12 hours after symptom onset, and only after confirming appropriate IVC placement by head CT and CSF outflow with normal pressure wave forms. No test article injections will be made until 1) at least six hours have passed to

allow for primary hemostasis after IVC placement and 2) a post-IVC placement CT confirms safe placement and clot stability.

A neurosurgeon or neurocritical care physician or their trained designee will perform IVC injections under standard sterile technique. All injections will be isovolemic (i.e. withdrawal volume equals test article plus flush volume). Viewing the coordinating center video demonstration of IVC injection protocol is mandatory before credentialing a center's physicians and coordinators. Ideally, injections will be preceded by gentle aspiration of up to 5 cc of CSF to minimize ICP elevation. Extracted CSF should be sent to the lab for safety evaluations once a day. Injection of the test article will be followed by up to 4.0 mL flush of normal saline.

Guidance for flush amount. The following recommendations are based on IVC tubing that is 33 cm in length and with an internal/external diameter of 1.7 mm/3.0 mm and commonly related ICP issues during dosing.

Two milliliters (2 cc) is thought to be sufficient to deliver test article into the ventricular system, but as specific situations can vary, if your IVC setup differs significantly from the above measurements you should calculate the volume of flush required to ensure intraventricular delivery of the study agent.

In all patients remove 4-10 cc of CSF. Removal of more CSF volume than you need to replace creates a net reduction of CSF intraventricular volume which may help with maintaining ICP control during the one hour closure period.

1. To clear the intravenous tubing and IVC of study agent, 2 cc of flush is recommended (based on 33 cm IVC and 33 cm of IV tubing between syringe and tip of IVC).

   If ICP is high prior to instillation of study agent, then ICP control measures should be instituted before treatment. Once control is achieved, instillation of study agent (1 cc) is appropriate, then administer at least 2.0 cc of flush and use additional medical management to attempt to control ICP or to maintain ICP control. If ICP still cannot be controlled open the IVC at a popoff of 25 mm Hg.

2. If removal of 4 cc CSF cannot be achieved, but ICP is controlled, clamp IVC to allow CSF accumulation, then retry in 1 hour and use 2 cc of flush.

3. If removal of 4 cc CSF still cannot be achieved, use 2 cc of flush. Treat any increase in ICP per protocol and if ICP cannot be controlled, open the IVC at a popoff of 25 mm Hg.

Each dose administration should be documented in the Medical Administration Record of the medical record as source documentation. A progress note should also be written in the medical record as source documentation to record the date and time of each dose, the amount of CSF withdrawn, the amount of test article administered, the amount of flush administered, the catheter in which the drug was administered (when more than one IVC is in place), the time the IVC was closed and reopened, the ICP, SBP, and DBP prior to the dose and prior to reopening the IVC, whether the IVC was closed to wean, and the name and title of the person who administered the dose.

ICU protocol to remove EVD. One hour after the last dose is administered the catheter should be opened for 24 hours to fully drain CSF and drug. Twenty-four hours after the last dose, weaning of EVD use may begin. If there is catheter tract bleeding prior to removal, wait 12 hours prior to removing catheter to allow for stabilization.

Adequate CSF circulation and resorption must be restored before the IVC can be safely removed. CSF resorptive capacity must be gauged according to CSF drainage rate. Adjusting the height of the drainage system drip chamber controls the rate of external CSF drainage, and hence the ICP that must be exceeded before the drainage occurs. The drip chamber is usually raised in 5-mmHg steps every 12 to 24 hours. As this is done, the CSF circulatory pathways and resorptive mechanisms are gradually challenged. If CSF circulation and resorption are insufficient, most of the CSF will continue to drain through the IVC, but if CSF resorption is sufficient, little CSF will drain externally. CSF resorption is usually considered inadequate if more than 200 to 250 cc CSF per day drains through the IVC with the drip chamber set at 15 mm Hg. When less than 100 cc of CSF drains per day, CSF drainage should be stopped and ICP should be monitored for 24 hours as final confirmation that spontaneous CSF resorption is adequate and ICP will not rise to dangerous levels. If ICP stays in an acceptable range, and there is no neurological deterioration, the IVC can be removed. If ICP increases in a sustained manner above 30 mm Hg, or there is neurological deterioration, the IVC should be reopened for further drainage or shunt surgery can be elected.

Daily CT Scan. A CT scan is required daily on days 1 through 5, and then repeated 1 and 3 days (approximately 24 and 72 hrs) post last dose of test article. During dosing, all patients must receive a minimum of one scan per day, preferably in the morning, but at least after every three doses are administered. This CT scan will monitor for clot lysis and asymptomatic bleeding and will be evaluated by the investigator prior to the next administration of test article. This does not represent an increase in the total number of scans requested; rather, it reflects two data collection goals: 1) to match drug administration times with independent assessment of safety and efficacy data points and to provide additional safety precautions during dosing; and 2) to collect the primary surrogate outcome measure on a fixed daily schedule for optimal measurement of the rate of clot resolution.

An unscheduled CT scan should also be done if the subject improves or worsens by more than two points on the GCS motor scale that is sustained for at least 8 hours, or sooner if clinically indicated.

The catheter tract must be reviewed on the daily CT scan to determine if there is a new onset or expansion of catheter tract hemorrhage.

The date and time of all daily and unscheduled CT scans should be recorded in the medical record as source documentation.

Vital Signs. Monitoring of vital signs includes documentation of blood pressure, GCS (to monitor for clinical improvement or neuroworsening), temperature, respiratory rate, heart rate, intubation status, ICP, CSF drainage, and drip chamber height. Therapy intensity levels will be documented jointly with the vital signs monitoring. Vital signs and therapy intensity levels are to be collected every 4 hours beginning at randomization through day 7. ICP data will be collected retrospectively back to the first

IVC placement and prospectively from enrollment through day 7. Beginning with day 8 and ending with the removal of the last IVC placed, a once daily assessment of ICP, total CSF drainage, and drip chamber height will be collected retrospectively at the 30 day follow-up visit, or sooner. These data will assess the subject's clinical response to treatment as part of the clinical trial as well as compliance with EVD discontinuation protocols.

All vital signs data must be recorded in the medical record, or as ICU monitor print outs as source documentation.

Lab Assessments. The results of daily white blood cell count, hematocrit, platelet count, aPTT, INR, CSF cultures, cell counts, protein, and glucose will be recorded. Lab assessments will be monitored through day 7. The following lab assessments must be done to screen the patient for eligibility: platelet count, INR, and, if applicable, urine or serum pregnancy test. The INR must remain ≤ 1.4 during dosing. Additionally, as a potential treatment response covariate, a lab assessment of plasma plasminogen activity and fibrinogen will be collected either at screening (if standard of care) or otherwise immediately prior to randomization following informed consent.

All lab results and sampling dates and times must be recorded in the medical record as source documentation.

NIHSS. The NIHSS should be done by a certified examiner as close to the time of randomization as possible, at Day 7, and again at months 1, 6, and 12.

The NIHSS results may be recorded directly on the electronic case report form.

Barthel Index. A historical Barthel Index score should be obtained to assess the patient's level of functioning, prior to symptom onset and will be used in a comparison with scores obtained at 1, 3, 6, 9, and 12 months.

The Barthel Index items and total score may be recorded directly on the electronic case report forms.

Modified Rankin Scale. A historical modified Rankin Scale score should be obtained as part of the screening procedures. The patient must have a mRS score of 0 or 1 to be eligible for the study. This historical score is based on the patient's level of functioning prior to the onset of symptoms and will be used in a comparison with scores obtained at 1, 3, 6, 9, and 12 months. The 1, 6, and 12 month evaluations will be done by a certified examiner and videotaped with digital images sent to the Outcome Coordinating Center at the Western Infirmary in Glasgow, UK.

The historical modified Rankin score may be recorded directly on the electronic case report forms. The Outcome Coordinating Center will adjudicate all follow-up modified Rankin scale scores.

Extended Glasgow Outcome Scale (GOSE). An Extended Glasgow Outcome Scale score should be obtained as part of the follow-up procedures at 1, 6, and 12 months. If the subject has a Mini-Mental exam score of 18-30, you should attempt to interview the subject. If the subject is unable to complete the

interview or has a Mini-Mental score < 18, then an appropriate caregiver should be interviewed to complete the GOSE. A GOS score will be computed by the Statistical Center from the GOSE scale.

The GOSE must be recorded on the bedside worksheets and then entered into the EDC. The bedside worksheets are required source documentation.

Stroke Impact Scale (SIS). A Stroke Impact Scale score should be obtained as part of the follow-up procedures at 1, 6, and 12 months. If the subject has a Mini-Mental exam score of 18-30, you should attempt to interview the subject. If the subject is unable to complete the interview or has a Mini-Mental score < 18, then an appropriate caregiver should be interviewed to complete the SIS.

The SIS must be recorded on the bedside worksheets and then entered into the EDC. The bedside worksheets are required source documentation.

Mini-Mental Exam. A Mini-Mental exam will be done as part of the follow-up procedures to determine the subject's ability to complete the GOSE and SIS interviews. If a subject has a Mini-Mental score of 18-30, subject interview will be attempted. If the subject is unable to complete the interview or has a Mini-Mental score < 18, then an appropriate caregiver should be interviewed to complete the GOSE and the SIS at 1, 6, and 12 months.

The Mini-Mental Exam may be recorded directly on the electronic case report forms.

Euro-Quol-5D. An EQ-5D score should be obtained as part of the follow-up procedures at 1, 3, 6, 9, and 12 months.

The EQ-5D must be recorded on the bedside worksheets and then entered into the EDC. The bedside worksheets are required source documentation.

Preference-Based Stroke Index. A PBSI score should be obtained as part of the follow-up procedures at 1, 6, and 12 months. If the subject has a Mini-Mental exam score of 18-30, you should attempt to interview the subject. If the subject is unable to complete the interview or has a Mini-Mental score < 18, then an appropriate caregiver should be interviewed to complete the PBSI.

The PBSI must be recorded on the bedside worksheets and then entered into the EDC. The bedside worksheets are required source documentation.

Personal Health Utility Assessment Interview. A Personal Health Utility Assessment Interview will be done as part of the follow-up procedures at 6 months.

The Interview must be recorded on the bedside worksheets and then entered into the EDC. The bedside worksheets are required source documentation.

Concomitant Treatments. All concomitant medications administered during active treatment (randomization through day 7) that are inclusive of the drug classes of interest will be recorded on the case report forms. This includes, but is not limited to: anti-hypertensives, sedatives, hypnotics,

hematologic modifiers, antiplatelet and anticoagulant medications, antibiotics and any other medication used to treat a neurological adverse event or any serious adverse event will be recorded through day 365.

11.6.4. Off-Intervention Requirements

Monitoring of all adverse events will continue through day 7. This includes monitoring of additional medications used, additional procedures and ICU care required. Serious adverse events, neurological adverse events, and hospitalizations related to neurological adverse events will be recorded at all follow up visits.

11.7. MANAGEMENT OF ADVERSE EXPERIENCES

11.7.1. Expected Adverse Experiences

The Medical Events listed below are published by the American Stroke Association and the European Stroke Initiative as natural history events of ICH/IVH or are found in the Investigator's Brochure or Alteplase Package Insert for the use of rt-PA. These medical events are therefore expected in the disease process or with use of the test article. Please enter these on the Medical Event form as adverse events. Reports of these events will be analyzed and submitted as grouped data by the trial's statisticians.

Expected Medical Events			
Nervous System		**Other Events**	
Brain Edema	Hydrocephalus	Aspiration	Pneumonia (Including ventilator-associated)
Brain Stem Compression	Hypoxia	Catheter-related vascular infections	Pulmonary Embolus
Brain Herniation	Intracranial Abscess	Deep Vein Thrombosis	Sepsis/Bacteremia
Brain Rebleeding Near the Initial Hemorrhage Site	Mass Effect	Diaschisis	Sinusitis
Catheter Tract bleeding/ Hemorrhage Enlargement	Meningitis, Bacterial or Non-Bacterial	Elevated BP	Spontaneous Bleeding from Non-cerebral sites
Cerebral Infarction	Perihematomal Ischemia	Fever/Hyperthermia	Thromboembolic Complications
Coma	Seizures	Hypercapnia	Urinary Tract Infections
Death	Ventriculitis, Bacterial or Non-Bacterial	Hypertension, Induced or Not Induced	Vascular Injury/Puncture Site Bleeding
Decreased LOC	Cerebritis	Hypotension, Induced or Not Induced	
Delirium		Infectious Complications	
Elevated ICP		Nausea/Vomiting	
Headache		Pericarditis	

11.7.2 Medical Events of Interest

Medical events of interest (MEOIs) must be reported to the CC for Safety Event Committee review.

1. Ventriculitis/Cerebritis/Meningitis
2. Cerebral bleeding events
3. Hydrocephalus requiring a VP shunt
4. Vascular thromboembolic events (DVT, PE) with clinical documentation and radiographic ultrasound confirmation [To be collected through acute hospital discharge only.]
5. AEs or SAEs related to a death within 30 days of enrollment into the trial
6. AEs or SAEs requiring discontinuation of dosing or withdrawal from follow-up

Compulsory SAEs. Certain AEs in the coding guide are defined as potentially serious SAEs if there is a medically qualifying factor. All AEs coded as a grade 4 or 5 will automatically require SAE reporting. These events will be reviewed by the Safety Event Committee.

11.7.3. Subject Management and Modification of the Study Intervention Regimen

Management of recurrent bleeding. Best care criteria defined by the AHA guidelines for management of ICH will be the standards of care for all general medical care in this protocol. Specifically, the guidelines are (1) Broderick JP, Connolly S, Feldman E: Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 2007;38:2001-2023, (2) European Stroke Initiative (EUSI) Guidelines for the management of intracranial hemorrhage (The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee. Recommendations for the Management of Intracranial Haemorrhage – Part I: Spontaneous Intracerebral Haemorrhage. Cerebrovascular Diseases 2006;22:294-316.), and (3) the AANS guidelines for management of elevated intracranial pressure (Bullock R, Chesnut RM, Clifton GL, et al. Brain Trauma Foundation, Inc, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. Guidelines for the management of severe traumatic brain injury: cerebral perfusion pressure. In. New York: Brain Trauma Foundation, Inc.; 2003. Adverse events will be managed similarly by employing these guidelines. Specific management for new intracranial bleeding does not exist. Each instance is managed by the care team as required to preserve life and function. Management may include blood pressure reduction, use of platelets and clotting factors, use of prothrombotic agents, and use of a surgical procedure. The management of each adverse event will be recorded and may be reviewed by the Safety Event Committee.

Management of ventriculitis. Routine antibiotic management of symptomatic ventriculitis (bacterial or non-bacterial) will be performed according to accepted principles of infection care. The selection of an antibiotic on the basis of culture and sensitivity data will be the primary means of management. Removal of any infected hardware and the subsequent adjustment of antibiotic on the basis of response to therapy will be applied to all patients. The management of each serious adverse event will be recorded and reviewed by the study Safety Event Committee.

11.7.4. Procedures for Modification

Test article will be discontinued for all symptomatic hemorrhage occurrences. No other modification of "best care" is anticipated for symptomatic hemorrhage. All care associated with this event will be recorded on the SAE eCRF. Test article will not be discontinued for ventriculitis. The same adverse event reporting will be employed.

11.8. Criteria for Intervention Discontinuation

Test article administration will be discontinued for any of the following reasons:

1. Dosing via the catheter contralateral to the clot will be discontinued when the 3rd and 4th ventricles are open. Dosing of the ipsilesional ventricle may continue if a second catheter is located in or near the residual blood. Dosing via this catheter may continue until an estimated 80% of intraventricular clot has been removed AND any IVH related mass effect (dilated or

shifted ventricle) is reversed, OR the subject receives 12 doses of test article (surgical endpoint), whichever occurs first
2. The subject experiences a clinically significant bleeding event (local or systemic) (treatment failure)
3. In the investigator's judgment, withdrawal from the trial would be in the subject's best interest. (treatment failure)
4. The subject or legal representative withdraws consent.

All subjects will be followed by the site team for 1year following the discontinuation of test article (reasons 1 to 4) as a part of the outcome assessment for the intervention. The use of the phone and mail will be the main means of maintaining contact after discharge. Follow up contact will be requested for patients that withdraw from the study. If this request is denied there will be no follow up of these patients.

11.9. STATISTICAL CONSIDERATIONS

11.9.1. Objectives of the Study

Primary Efficacy. The primary objective of this multicenter, international, randomized, controlled, Phase III study with double-blinded evaluations is to define precisely the long-term effect of active treatment with EVD + rt-PA versus EVD + placebo (saline vehicle) for removal of ventricular blood clot on the functional outcome of cerebral hemorrhage patients. We propose to test if this intervention promotes an improved level of function as defined by a mRS of ≤ 3, by facilitating more rapid clot resolution, as compared to treatment with EVD + placebo. Although the mRS includes a category for death, and hence the primary analysis incorporates mortality outcomes, mortality as a separate outcome will also be examined. An intent-to-treat paradigm for the analyses will be incorporated, counting all patients who are randomized and receive at least the first dose. This study is powered to test the primary hypothesis that EVD coupled with rt-PA treatment produces improvements in outcome as measured by a dichotomized mRS (defined as a mRS score of ≤ 3 at 180 days post ictus).

Secondary Efficacy. Secondary measures of efficacy include the mRS score on the ordinal (0-6) scale as well as the 0-4 vs 5-6 dichotomy, mortality at 180 days post treatment, amount of residual blood at 72 hours, rate of blood removal, intensity of critical care management as measured by length of hospital and ICU stay, duration of EVD, intensity of ICP management, rate of needing permanent ventriculoperitoneal shunt, and frequency of general medical care complications. Measures of functional outcome and quality of life will include: the Barthel Index; the extended GOS (GOSE); the Stroke Impact Scale; the Preference-Based Stroke Index (PBSI); the Mini-Mental Exam; and the EQ-5D (EuroQOL) at 1, 3, 6, 9, and 12 months; the NIHSS at 1, 6, and 12 months; length of stay (LOS) and time at home in the first 180 days after hospitalization.

Efficacy Measures Summary.

- **Primary:**

Dichotomized mRS 0-3 vs. 4-6 at 180 days

- **Secondary measures**

1. Additional mRS Dichotomizations at 180 days (0-4 vs 5-6)
2. Ordinal mRS (0 – 6)
3. Mortality and Safety Events at 30 days
4. Mortality at 180 days
5. Functional Status: NIHSS, Barthel Index, GOS, extended GOS, mRS, Personal Health Utility Assessment Interview
6. Type and Intensity of ICU Management: ICU days, CSF drainage time, ICP management intensity, EVD weaning time, number of critical care complications
7. Rate and extent of ventricular blood clot removal based on CT Imaging
8. Quality of Life: Stroke Impact Scale, EQ-5D, PBSI, LOS (acute care + rehab); time at home during first 180 days

In addition to the primary and secondary measures, there are a number of related and intermediate surrogate outcomes of interest, including Glasgow Coma Score (GCS), ICU time, hospital time, discharge time, Graeb Scale, clot lysis rate and final clot size reduction.

Safety. Two general safety concerns have been voiced by expert clinicians: 1) injections of rt-PA should not compromise intracranial pressure (ICP) management; and 2) the risk of additional bleeding should be minimized by protocol design. To monitor these and other safety concerns, interim safety analyses will be prepared for the external Data and Safety Monitoring Board (DSMB) on a pre-arranged schedule (such as semi-annually or after enrollment of a fixed number of subjects) to evaluate efficacy and safety. Safety measures include: monitoring incidence of symptomatic and asymptomatic intracranial bleeding events (i.e., hemorrhage extension, new hemorrhage, catheter tract hemorrhage) through daily computerized tomography (CT) scans for the first 5 days after enrollment and 1 and 3 days (about 24 and 72 h) post last dose, maintenance of INR $\leq$ 1.4 during dosing, monitoring the incidence of confirmed and suspected infection through daily cultures of CSF withdrawn from the intraventricular catheter, and 30-day mortality.

Safety Monitoring and Recruitment Suspension Rules. Recruitment to the trial will be suspended if a threshold level is exceeded for the events of death prior to day 30 following symptom onset (40%), symptomatic re-bleeding within 72 hours of last dose (25%) and bacterial infection within 72 hours of last dose (20%) for either treatment group. The suggested suspension rule is based on Fleming's design,[61] and is based on rejection points (number of subjects with the observed adverse event of interest) calculated for each of the looks at the accumulating data. Note that the numbers of subjects with observed events that trigger suspension at each look are extreme compared to the overall number of events expected by multiplying the total sample size times the threshold percentage; this is due to the sequential nature of the testing which retains the overall significance level of 0.05 by the end of the study. We assume that the total number of subjects enrolled per 6 months in a single treatment group is 30; thus, 8 semi-annual looks at the data are projected. Suspension of recruitment will occur if the event frequency exceeds the indicated number of subjects with adverse events.

11.9.2. Randomization

The study is a two-arm, adaptively-randomized design whereby eligible patients are randomized to treatment with EVD + rt-PA or EVD + placebo. The randomization scheme is said to be adaptive,

because patients will have a weighted chance of being randomized to each treatment arm based upon the distribution of key severity factors (including IVH size and ICH location) of previously enrolled subjects at the time of the enrollment. For example, if at any given time there are more patients with large IVH (> 40 cc) in the placebo group at the time when a candidate with large IVH is being screening, then the screened candidate will have a greater likelihood of being randomized to active treatment versus placebo. This design ensures that at the end of the study, there will be an equal distribution of known severity factors between the treatment groups. To ensure early treatment allocation balance at a given site, subjects will be block-randomized in 2:2 (active treatment:placebo) blocks for the first four subjects at each site; the fifth enrollment, and all subsequent enrollments will be randomized using the adaptive randomization scheme.

Once a patient is determined to be potentially eligible for participation in the study, the site coordinator or a designated member of the study team at the site will enter the Inclusion/Exclusion information about the study subject into the VISION (Prelude Dynamics, Austin, Texas) web-based electronic case report form (eCRF) system. Information required for adaptive randomization includes ICH location and IVH volume. IVH volume will be calculated by a trained image technician at the Reading Center using DICOM images provided by the site and validated image measurement tools for highly accurate IVH volume measurements. In the event that DICOM images are not available to the Reading Center at the time of randomization, an approximation of the IVH volume will be used, which incorporates the modified Graeb IVH score, and the gender and age of the subject.The VISION system will process these subject variables, determine eligibility and, if eligible, assign an identification number and treatment method to the patient. The randomization process is handled by an embedded software module; this module is part of the system and is invoked by the coordinator or investigator within the eCRF system. Randomization is triggered by the investigator or coordinator, via completion of a form in the eCRF, after all eligibility checks are performed. If the coordinator/investigator checks the randomize box and saves the form, the system will automatically set the enrollment date, assign a study ID and trigger the embedded randomization algorithm to determine the randomized treatment (including a final check to make sure the patient is still eligible). The implementation will be independently tested by the Biostatistics Center. The site coordinator is provided with a unique, blinded electronic treatment assignment number (randomized patient number) at the end of this process.

11.9.3. Blinding

At the time of randomization, the coordinator/investigator will select the name of a qualified pharmacist (or alternatively the location of a secure pharmacy fax machine) from a drop-down list in the eCRF. The list of qualified pharmacist names and email addresses (or fax numbers) will have been previously entered into the system securely by someone at the coordinating center to prevent malicious unblinding by falsifying the pharmacist's email address. Upon randomization, the eCRF will transmit a confidential notification (by email or fax) directly to the selected pharmacist identifying the patient and stating whether the patient will receive active drug or placebo. As a backup and secondary security measure, an identical notification will simultaneously be sent to the unblinded Trial Pharmacist at the CC. The system will also send an email to the investigator, coordinator and CC staff confirming that a patient has been randomized, but this email will not contain the test article code (active drug or placebo). All notifications are sent directly from the eCRF system (from a server in Austin, Texas) only to pre-defined email addresses (or email-to-fax phone numbers) that were previously verified by the coordinating

center. The eCRF will not disclose the test article to anyone other than the unblinded Trial Pharmacist at the Coordinating Center and the local pharmacist as selected from the pre-defined drop-down list.

The pharmacist will provide the appropriate test article as a blinded substance to the responsible caregivers at the subject's site within the hospital. In this way the site coordinator, physician and patient remain blinded to the treatment assignment.

The certified examiner performing the 1, 6, and 9 month follow-up assessments will video tape the mRS assessments and upload the video to Glasgow where trained reviewers in Glasgow will classify the interview objectively without knowledge of the examiner's score or of the treatment details including treatment intensity.

11.9.4. Target Population and Study Samples

i. **Target Population.** The target population to which the EVD + rt-PA therapy or EVD + placebo may be applied are patients with IVH secondary to supratentorial ICH, and without suspected underlying structural etiology (tumor, vascular malformation or aneurysm). Patients have IVH obstruction in the 3rd or 4th ventricle and an ICH $\leq$ 35 cc ($\leq$ 30 cc at the time of diagnosis), that is stable.

ii. **Intent-to-Treat Sample.** As the primary analysis, all efficacy and safety outcome measures are analyzed under the ITT. Under this principle, the evaluable sample includes all subjects who are randomized and who receive at least one dose of test article. Each subject is analyzed according to the treatment group to which they were assigned at the time of randomization.

iii. **Safety Analysis Sample.** All randomized subjects are included in the safety analysis sample.

iv. **Per-Protocol Sample.** The potential for cross-overs in this study is minimal; none have occurred to date. However, in the case of cross-overs, a per-protocol sample will be constructed and examined in which treatment-as-received is analyzed. Given that clot resolution is a potentially treatment-related post-randomization variable, clot resolution will be examined as an important potential mediator of final outcomes as part of a per-protocol analysis.

11.9.5. Overall Methodology Description

The initial stage of analysis is data cleaning, variable development, and exploratory data analyses (EDA). All variables will be evaluated to detect gaps, patterns, and inconsistencies in the data. The frequency distributions of categorical data will be described. Continuous variables will be described in terms of their centrality, spread, shape, and possible outliers. These analyses will emphasize examination of the nature and extent of variability for all variables. Visual techniques to explore continuous variables will include stem-and-leaf plots, box plots, and quantile-quantile plots. Outliers will additionally be examined for possible data entry errors. Summary statistics for continuous variables will include the number of patients, mean, standard deviation, minimum, median, and maximum. Summary statistics for categorical variables will include the frequency and percentage of patients in each category. Data will be summarized by treatment group (blinded for any interim analyses) and total patient population. All assessments before the first dose of study drug will be considered as Baseline.

Analyses will proceed in two phases; i.) cross-sectional evaluations (30 day mortality and safety events, 180 day outcomes, etc.), and ii.) full longitudinal evaluations. The first phase will compare 180-day outcomes for subjects receiving EVD + rt-PA (intervention) treatment against subjects receiving EVD + placebo. Analyses for these comparisons will be guided by exploratory analyses. Logistic regression will be used to assess treatment differences in the primary dichotomized outcome (mRS $\leq$3 vs. >3) and will account for design aspects such as potential within-site clustering. Since dichotomization of categorical measures results in a loss of efficiency and power, appropriate categorical data analysis techniques (such as generalized logit, proportional odds and two-stage models) will be performed to retain use of the full ordinal outcome scales and maximize power to capture intervention effects. Generalized linear model formulations also allow investigation into other explanatory variable confounding as well as moderating and mediation effects. ICH volume and location, clot resolution rate mediation effects, and differential gender and age effects will specifically be examined.

The second phase of analysis will examine outcomes in terms of longitudinal components, using data collected at initial entry into the study, ICU discharge, and follow-up at 1, 3, 6, 9, and 12 months. These data will contain within-subject correlations from one time point to the next. Since the overall goal of the trial is to compare subjects receiving the intervention of EVD + rt-PA with subjects receiving EVD + placebo, a marginal model estimated using a generalized estimating equations (GEE) technique is appropriate.[62] The GEE technique requires specification of the standard 'mean' model, as well as specification of a working 'association' model. One strength of the technique is that the parameters of main interest in the mean model (i.e. the intervention effect) are consistent regardless of whether the association model is specified correctly. All analyses will initially be examined with a working independence assumption. When the entire model is specified correctly, optimally efficient estimates are obtained. Hence, analyses will be augmented with Toeplitz-type and autoregressive-type working correlation matrices. Generalized Linear Mixed Models (GLMMs) may also be examined to provide subject and site-specific effects. Analyses for specific hypotheses follow below.

11.9.6. Patient Disposition

Summary statistics will be presented for the analysis sets and subgroups, the patients who completed the study, the patients who discontinued early from the study, and the reasons for early discontinuation including bleeding, loss to follow up, patient withdrawal or refusal, other complicating disease, error, or other reasons.

11.9.7. Baseline Characteristics

i. **Demographics.** Summary statistics will be presented for age (years), gender (male or female), race and ethnicity, presentation center, pertinent medical history including illicit drug use, hypertension history, diabetes, anticoagulation, and antiplatelet drug use.

ii. **Medical History.** Summary statistics will be presented for medical history, as well as presentation temperature, pulse, systolic blood pressure, and diastolic blood pressure. Presenting NIHSS, ICP, ICH volume, IVH volume, location of bleed and IVH score will be provided.

11.9.8. Efficacy Analyses

11.9.8.1. Primary Outcome: Modified Rankin Scale ≤ 3 at 180 days

1a) Hypothesis 1.1: The primary hypothesis is that clot removal with EVD + rt-PA can increase the percent of patients with a good functional outcome, compared to management with EVD + placebo.

1b) Analyses: The primary comparison is a dichotomized comparison of the 180 day mRS scale: 0-3 vs. 4-6 which is predicated on the preliminary data from earlier CLEAR IVH trials. The primary analysis will be a direct comparison using an intent-to-treat analysis of dichotomized mRS by treatment group and a logistic regression model with one covariate, treatment. Subsequently the more extensive data modeling will be used as suggested to explore all the effects of severity factors and co-morbidity on functional outcomes

The next evaluation of Hypothesis 1.1 will be to examine differences between dichotomized mRS scores (such as mRS ≤ 3) between the EVD + rt-PA and EVD + placebo groups using a logistic regression model of the form:

$$\log\left(\frac{p}{1-p}\right) = \alpha_0 + \beta X + \theta \cdot TRT$$

where: p = Prob (function recovery), α_0 is an intercept parameter (i.e. log-odds of function recovery under EVD + placebo), β is a vector of regression coefficients pertaining to relative effects of interest such as initial clot size, ICH clot location, etc., as incorporated in the covariate matrix X, and θ is the treatment effect parameter for EVD + rt-PA. These formulations allow similar alternative models to be entertained as well, such as stronger treatment effects in some clot locations as compared to others, and sensitivity towards functional assessments and including/excluding death in the scale. Note that the mean model pertaining to 180-day outcomes has been specified, as specification of the longitudinal models is similar with the addition of working 'association' aspects and potential time-dependent effects.

1c) Additional Efficacy Analyses of the Primary Outcome: Accounting for Clinical Center Effects: Center effects will be examined as both fixed effects in the GLM framework above and random effects, incorporated through a GLMM framework. Given the expected 30-75 centers, variation between centers should be well estimable. Probit-link GLMMs may be utilized to facilitate marginalization of the desired population-averaged treatment effects.[63]

Subgroup Analyses. Patients with more severe characteristics at presentation may be at risk of worse outcomes regardless of randomization group. A severity indicator or index will be constructed based upon presentation characteristics such as IVH size, ICH size, clot location, age, and gender, and potential differences in treatment effects across severity levels will be examined.

11.9.8.2. Secondary Outcomes

a. Alternate mRS cutoffs at 180 days: (mRS ≤ 4)

1) Hypothesis 2.0: Clot removal with EVD + rt-PA can increase the percent of patients with a good functional outcome, compared to management with EVD + placebo. For a disease with very high mortality, the 0-3 and 0-4 thresholds are the critical thresholds for evaluating a biologic benefit of intervention.[64] Thus, these will be examined first. There is some degree of controversy in the literature regarding the choice of mRS cutoff thresholds. Thus, the treatment effects for alternate definitions of "good outcome" also will be estimated.

2) Analyses: Analyses will be similar to the primary outcome analyses above.

b. Ordinal mRS

1) Hypothesis 2.1: EVD+ rt-PA for IVH clot removal produces improved outcome(s) assessed by the ordinal mRS score when compared to EVD + placebo.

2) Analyses: To retain information in the full ordinal mRS, a proportional odds model will be estimated of the form:

$$\log\left(\frac{\gamma_k}{1-\gamma_k}\right) = \alpha_k + \beta X + \theta \cdot TRT$$

where: α_k = Prob(mRS $\leq$ k), k=0,1,...,5

The proportional odds model is very similar to the logistic regression model described above, with the difference being that the interpretation of the estimated treatment effect considers the likelihood of a patient being in any subsequently lower mRS category. The set of intercepts, α_k k=0, 1,..., 5, are now initial cumulative probabilities which incorporate all outcomes below any given level, covariates are again included through β and X, and the treatment difference θ now describes the log-odds of moving from any cumulatively higher (worse) category, into any cumulatively lower (better) category. For instance, here θ describes both how the intervention moves patients from the mRS category of 'Dead' (6), to 'living' (0-5), as well as how the intervention moves patients from 'Severe Disability or Dead' (5,6) to 'No Symptoms through Moderate Disability' (0-4) and so forth. This model is more efficient than the simple dichotomous approach since it uses the available information across the entire scale of the measure. To examine the proportional odds assumption, generalized logistic models that replace β and θ with β_k and θ_k will be used, allowing non-parallel effects between successive cumulative categories. In the event that the proportional odds assumption is rejected, results from the generalized logistic models will be presented.

c. Mortality and Safety Events at 30 days

1) Hypothesis 2.2: Mortality attributed to EVD + rt-PA treatment plus disease–associated adverse events are similar to the morbidity and mortality attributed to EVD + placebo in the first 30 days.

2) Analyses: For initial evaluations of secondary Hypothesis 2.2, differences between the EVD + rt-PA intervention and EVD + placebo groups will be examined using a logistic regression model similar to that shown above for Hypothesis 1.1.

d. Mortality at 180 days

1) Hypothesis 2.3: Mortality at 180 days post treatment for EVD + rt-PA treated patients will be improved as compared to that of patients managed with EVD + placebo.

2) Analyses: For initial evaluations of secondary Hypothesis 2.3, differences between the EVD + rt-PA and EVD + placebo groups will be examined using a logistic regression model similar to that shown above for Hypothesis 1.1.

e. Functional Status:

1) Hypothesis 2.4: Clot removal with EVD + rt-PA treatment produces improvements in **functional outcome** assessed by alternative outcome measures such as NIHSS, Barthel Index, Glasgow Outcomes Scale, extended Glasgow Outcomes Scale and mRS.

2) Analyses: Linear, logistic and polytomous data models to examine secondary Hypothesis 2.4 will be similar to those presented above.

f. Type and Intensity of ICU Management

1) Hypothesis 2.5: EVD + rt-PA treatment of IVH leads to decreased intensity of hospital care compared to EVD + placebo. This includes fewer hospital days, ICU days, decreased intensity of ICP management, shorter periods of CSF drainage, lower utilization of ventriculoperitoneal shunts, and fewer general critical care complications.

2) Analyses: Linear, log-linear, and logistic data models to examine secondary Hypothesis 2.5 will be similar to those presented above.

g. Effects of rate and extent of ventricular blood clot removal

1) Hypothesis 2.6: The amount of residual blood at 72 hours and removal rates are associated with functional outcome at 180 days post bleed.

2) Analyses: For initial evaluation of secondary Hypothesis 2.6, associations with removal amounts and rates across and within the EVD + rt-PA and EVD + placebo groups for the primary outcome will be examined using a logistic regression model similar to that shown above for Hypothesis 1.1.

h. Quality of Life

1) Hypothesis 2.7: Quality of Life (QOL). Clot removal with EVD + rt-PA leads to improved health related QOL as assessed by subject and surrogate QOL domains through the Stroke Impact Scale, EQ-5D, PBSI, and time at home endpoints.

2) Analyses: Linear, logistic and polytomous data models to examine secondary Hypothesis 2.7 will be similar to those presented above.

11.9.8.3. Additional Efficacy Analyses: Additionally, survival models will be constructed to examine the mortality, morbidity and ICU distributions for the EVD + rt-PA and EVD + placebo groups. Standard Cox proportional hazard models will initially be examined. These models are commonly written as:

$$h_i(t) = \lambda_0(t)\exp(\gamma X + \phi \cdot TRT)$$

where $\lambda_0(t)$ is a non-parametric baseline hazard function, γ is again a vector of regression coefficients related to the X covariates and ϕ is the parameter for the treatment effect of EVD + rt-PA on the hazard of death (mortality). This model may be extended by including time-dependent covariates and non-proportional hazards as deemed necessary through diagnostic checks. Observed mortality will also be compared with predicted mortality based on clinical presentation, overall and by treatment group. Predicted mortality will be estimated using the most recent Tuhrim model which takes IVH volume and presence of hydrocephalus into account.[26]

11.9.8.4. Additional Analyses of Intermediate Surrogate Outcomes. Methods similar to those mentioned above will be used to additionally describe and compare the two patient groups for characteristics such as length of stay, BP and ICP during treatment, level of consciousness (GCS), and clot resolution rate. Analyses that have examined the relationship of individual patient's rate of clot resolution with change in GCS have shown that increased rates of clot resolution are associated with greater improvements in GCS during the first few days of treatment. Similarly, analyses on the 64 patients from the safety study and CLEAR IVH A studies has shown that rate of clot resolution is associated with better outcomes on the mRS. This relationship also appears for the CLEAR IVH B study. Mediation effects of clot resolution rates on the relationship between intervention and outcomes will be characterized by contrasting our primary outcome models with and without inclusion of clot resolution rate terms. As mentioned above, other explanatory variable-confounding, moderating and mediation effects will be investigated, and ICH volume and primary bleeding location, clot resolution rate mediation effects, and differential gender and age effects will specifically be examined.

Until now, controlled clinical studies have not routinely quantified the rate of resolution of the IVH clot during the first few days of treatment. In this study the amount of clot remaining at both 72 h and at 96 h will be examined, and methods developed for our studies of IVH patients to examine the rate of clot resolution early in the treatment will be used. The volumes from the stability CT and all CTs up to and including those taken 96 h immediately following the stability CT will be considered. Since the aim of active treatment is to achieve rapid removal of the clot, some analyses will be limited to the first 72 h. In any such analyses initial IVH volume will be taken into account since there will be a wide variation in initial clot volumes and our current evidence shows that volume of IVH clot resolved per day is strongly related to the initial volume.[32] Repeated observations per patient will again be taken into account using

GEE techniques, undertaken with the centrally measured IVH clot volumes and the simpler site-derived Graeb scores.

11.9.9. Safety Analyses

The primary safety measures for this study are symptomatic intracranial bleeding and infection occurring ≤ 72 hours post last dose and death occurring ≤ 30 days post symptom onset. As ICP control is one of the main problems with this population, the degree of ICP elevation by duration and magnitude of elevation will be examined.

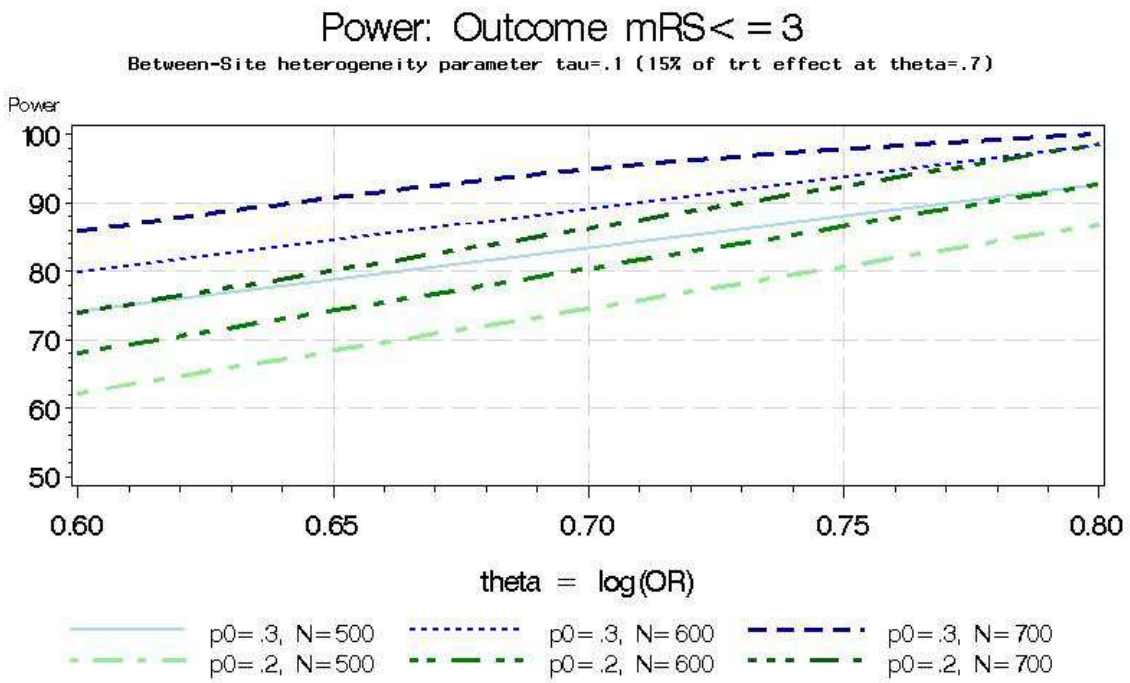
11.9.9.1. Adverse Events and Serious Adverse Events. All AEs and SAEs are summarized by type and by treatment group in terms of frequency of the event, number of subjects having the event, timing relative to randomization, severity (mild, moderate, severe), and relatedness to the study treatment (definitely, probably, possibly, definitely not). At the end of the study, the cumulative incidences of these events will be compared between the two treatment groups using Fisher's exact test. Additionally, generalized linear mixed models for binary data will be used to examine AE and SAE probabilities between treatment groups while accounting for potential confounders and center clustering effects.

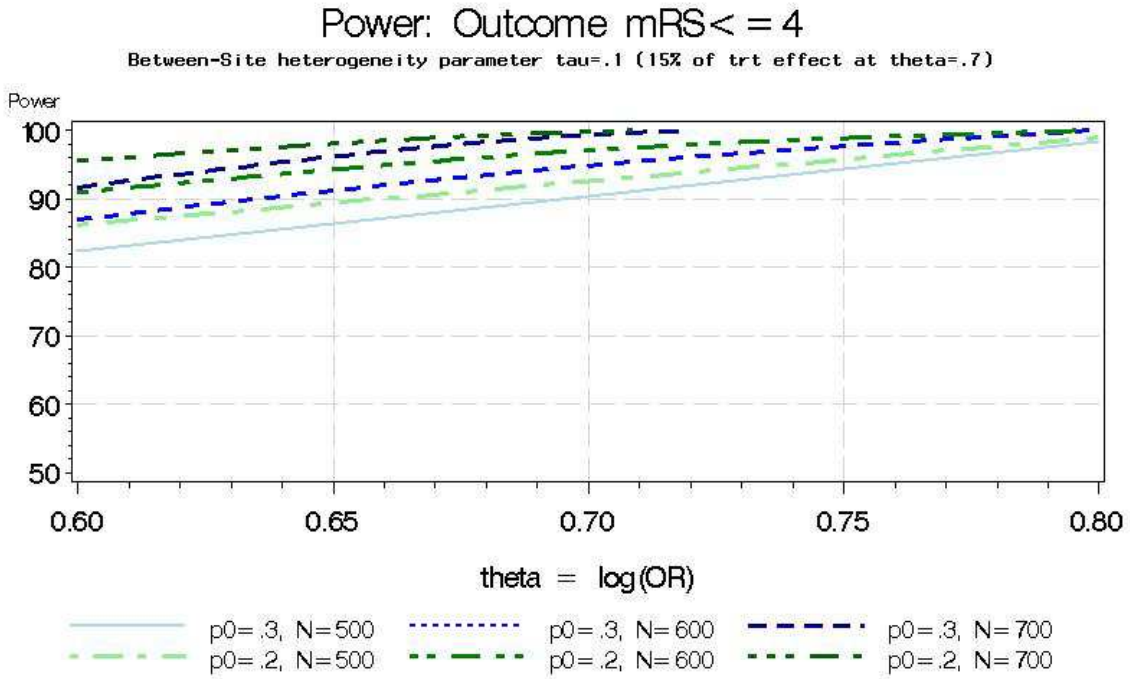
11.9.9.2. Time to Death and Time to Re-Bleed. As a secondary assessment, time to death or re-bleed within the one-year follow up period are compared between the EVD + rt-PA and EVD + placebo groups adjusting for appropriate baseline covariates. Provided the model assumptions are met, a proportional hazards regression model may be used for the analysis as described above

11.9.9.3. Safety Monitoring. The BC will generate periodic DSMB reports (We assume that the total number of subjects enrolled per 6 months in a single treatment group will be approximately 30; thus, 8 semi-annual looks at the data will be suggested to the DSMB. As usual though, periods for reporting will be discussed and finalized at the initial DSMB meeting). Each report will provide cumulative summary statistics on enrollment; subject status in the study (e.g., number completed at 3-month, 6-month, 9-month, and 12-month assessments); baseline characteristics; protocol violations; safety data, including AEs and SAEs by AE code, severity, and relatedness to the study medication; outcomes data (if coinciding with an interim analysis – also to be discussed and finalized at the initial DSMB meeting); and data management/quality information (e.g., timeliness and completeness of data entry by the clinical centers via the CLEAR III Trial Website; number of DCRs generated and resolved). Two reports will be generated, an open report with combined data from both treatment groups, and a closed report for the DSMB voting committee members with data provided by blinded treatment group. The outline of these proposed DSMB reports is included in the Manual of Operations and Procedures (Chapter 21: Data Safety and Monitoring Board). In an interval as yet to be determined (monthly or quarterly), the CC will also generate a Safety Monitoring Report to be distributed to the DSMB. This report contains only the enrollment, subject study status, safety, and data quality information. The Executive Committee also receives the Safety Monitoring Reports. The DSMB will have discretion to recommend stopping the trial early if safety concerns become substantial. The Steering committee has the ultimate authority to stop the investigation for safety or any other reason.

11.9.10. Sample Size Determination

Our projected sample size is 500 (250 in each treatment group). Primary sample size/power calculations were based on Monte Carlo simulations using the modeling framework outlined above. A variety of simulation scenarios were examined to judge the sensitivity of power towards sample size (N=500, 600, and 700), effect size (odds-ratio=1.8 to 2.2), control group outcome rates (placebo rates of good outcome mRS≤3=20%, 30%), model choice (correctly specified vs non-correctly specified model), and site clustering (between site heterogeneity parameterized as a latent effect with standard deviation τ=0.1 and 0.25 {i.e. 14%, 36% of log-odds-ratio treatment effect = 0.7, (OR=2.0), respectively}). The total projected sample size of 500 provides 80% or greater power to detect an increase in the odds of 92% (OR=1.92) or more for having a better mRS primary outcome (mRS score ≤ 3) for clot removal with EVD + rt-PA versus EVD + placebo, controlling for IVH & ICH volume and clot location and assuming a two-sided significance level of 5%. This corresponds to detecting an absolute difference of 13% or more in the probability of better outcomes comparing EVD + rt-PA vs EVD + placebo with control rates around 25%. Given our observed rates from the Safety, CLEAR IVH A and CLEAR IVH B studies of 15-17%, this sample size adequately powers the study. For the secondary binary outcome of mRS≤4, a sample size of 500 has at least 80% power to detect an increase in the odds by 82% (OR=1.82) or more. The figures below summarize the main findings of the Monte Carlo study.





Power curves from dichotomous mRS endpoints across varying levels of sample size and treatment effect theta=log(OR) for between site heterogeneity parameter τ=.1 (14% the effect size of the treatment effect theta at theta=.7). For N=500, power is greater than 80% for combinations of parameters near those observed in current studies (p0=.25, theta=.7).

Additional simulations were performed to examine sensitivity towards effects of a potential latent patient-severity factor based on an IVH volume > 60 cc. Inclusion of this factor in the simulation methodology did not change the overall power results.

In addition to the Monte Carlo simulations above, we may investigate power for the primary Hypothesis for a study designed to enroll a total of 500 patients through standard asymptotic rate comparison power formulae. The power available to detect various effect sizes is shown below for ranges between 20% to 35% of the current EVD + placebo group achieving a good outcome (such as mRS score ≤ 3) calculated using the normal approximation with continuity correction for a two sample test of equality of proportions.

Power Available to Detect Specified Effect With Alpha = 0.05 For Two Groups of Size 250 (Total of 500 patients)				
Proportion with Good Outcome in the EVD alone Management Group				
Effect size (Abs diff.)	20%	25%	30%	35%
25%	>.99	>.99	>.99	>.99
20%	>.99	>.99	>.99	>.99
15%	.96	.94	.92	.91
14%	.93	.91	.88	.87
13%	.89	.86	.84	.82
12%	.84	.80	.77	.75
11%	.78	.73	.70	.68
10%	.70	.65	.61	.59

Thus, with a total sample size of 500, the power is 80% or higher to detect differences in mRS outcomes of 13% or greater, assuming a two-sided significance level of 5% and control rates of 20% to 35% in the EVD + placebo group.

11.9.11. Innovative Methods

Categorical outcomes such as the mRS, GOS, etc, are termed composite outcomes in the statistical literature as they combine outcomes of interest such as ability/disability with mortality outcomes. There have been recent methods developed to allow simultaneous examination of the ability/disability and mortality outcomes but they do not specifically include mortality in the actual outcome scale. Joint analyses based on generalized linear mixed models (GLMM) have been introduced,[65] and are proposed to extend these models for the brain injury/stroke literature using data from this trial. A latent Gaussian process will be posited to represent an individual's underlying propensity to regain ability which describes relationships between a subject's longitudinal outcomes. A random effects model corresponding to the dichotomous mRS logistic regression model outlined above may be specified as:

$$\text{1) R.E. model:} \quad \text{logit}\{ \Pr(R_{ij} \mid a_i) \} = \alpha_0 + \beta X_i + \theta \text{TRT} + a_i$$
$$\text{2) Latent Effect:} \quad a_i \sim N(0,\tau^2) \qquad \text{(Exchangeable)}$$

where R_{ij} is the binary outcome for patient i at time j and R_{ij}=1 if $mRS_{ij} \leq 2$ and R_{ij}=0 if $3 \geq mRS_{ij} \geq 5$. Note that the category mRS_{ij}=6, indicating death, has been removed from the outcome definition such that R_{ij} describes ability for those remaining alive at time j. In addition to this model, Cox Proportional Hazards

Model (PHM) for mortality described above will be investigated, as well as possibly three parametric survival models (exponential, Weibull and log-logistic). For subject *i*, the Cox PHM specifies the dependence of survival on treatment through an instantaneous hazard function at time *j* of:

$$\text{Cox PHM:} \quad \log\{ h_i(j) \} = \log\{ \lambda_0(j) \} + \gamma X_i + \phi \text{TRT}$$

A corresponding Weibull survival model with parametric baseline hazard may be specified in two equivalent ways:

$$\text{1) Weibull Model:} \quad \log\{ h_i(j) \} = \delta \log(j) + \gamma X_i + \phi \text{TRT}$$
$$\text{2) Weibull Model:} \quad \log\{ J_i \} = \gamma_0 + \gamma X_i + \phi \text{TRT} + \sigma\varepsilon$$

where ε is the disturbance term from a 2-parameter extreme-value distribution. The equivalence between the hazard specification and the log-time specification is given by: $\gamma^* = -\gamma / \sigma$.

If treatment is related to both ability and mortality/time in study, an attenuation of the effects of treatment on the ability measure may be seen, using the logistic GLMM proposed above. To address this issue a parametric joint longitudinal-survival model may be used that ties the separate aspects together via the latent Gaussian process introduced previously.

$$\text{1) R.E. logistic model:} \quad \text{logit}\{ \Pr(R_{ij} \mid a_i) \} = \alpha_0 + \beta X_i + \theta \text{TRT} + a_i$$
$$\text{2) Weibull Survival Model:} \quad \log\{ h_i(j) \} = \delta \log(j) + \gamma X_i + \phi \text{TRT} + \rho \cdot a_i$$
$$\text{3) Latent Effect:} \quad a_i \sim N(0, \tau^2)$$

The additional parameter ρ assesses the association between the longitudinal logistic-regression model and the survival hazard-regression model generated by the latent process. GLMMs are known to give conditional, subject-specific inferences rather than the marginal treatment effect inferences desired for a clinical trial as discussed earlier. The differences between subject-specific and marginal inferences are most pronounced when using logistic models. Griswold & Zeger[66] and Caffo & Griswold[63] show how to obtain marginal estimates from GLMMs by appropriately specifying the latent model aspect. The data in the proposed trial will be fundamental to evaluating these models for use in brain hemorrhage and trial research, as well as developing extensions of these methods to polytomous ability models.

11.9.12. Missing Data

Minimal loss to follow up for the 6-month assessment of the primary outcome is expected, based on our previous studies with this group of stroke patients (observed experience of 2% missing). Substantial efforts will be made to ensure complete follow up, such as collection of contact information for patients and patient surrogates for collection of outcome measures. All efficacy outcome measures will be analyzed under the intent-to-treat principle, and the sample analyzed will include all randomized subjects who receive at least one dose of test article. Rates of missing data and losses to follow-up will be reported and effects of incompleteness/noncompliance will be quantified through sensitivity analyses,[67] the gold standard in the field.

11.9.13. Outliers, Noncompliance, Multiplicity & Interim Analyses

Outliers for primary outcomes should not cause concern for this study as the outcomes are categorical in nature. For other continuous outcomes examined in this study, outliers will be examined for validity,

incorporated in and removed from primary models to assess sensitivity, and potentially transformed to another scale or modeled with skewed distributions depending on appropriateness.

Noncompliance should not cause concern for this study as the randomization by center should minimize treatment cross-over. Any effects of noncompliance that do arise will be examined by contrasting the per-protocol and intent-to-treat analyses.

The study design for the primary comparison is a two-arm randomized trial with a single treatment contrast, hence, multiplicity from several tests is not an issue.

The Johns Hopkins Biostatistics Center will generate blinded periodic interim reports on efficacy for the DSMB after a pre-established number of patients have been recruited. To eliminate statistical paradoxes that may arise with multiple look group-sequential testing rules, we will propose to the DSMB to use evidence based likelihood intervals rather than confidence intervals to depict the blinded group differences. This evidential technique allows us to represent the information accumulated in the data at each reporting period while avoiding difficulties inherent in multiple look decision rule classifications based on frequentist theory.[68] The monitoring approach will be discussed and formalized at the first DSMB meeting. If an alternative approach is preferred, group-sequential stopping boundaries will be used.

11.10. Data Collection, Site Monitoring, and Adverse Experience Reporting

11.10.1. Records to Be Kept

Records Retention. Participation in this study requires that original study documents be retained for a minimum of 2 years following notification of the FDA by the study CC that investigations have been discontinued. This standard complies with U.S. FDA regulations (21 CFR §312.62[c]). Records must not be destroyed without first contacting the CC to ensure that the time limits defined in the regulations have been met. Study centers in countries other than the US participating in the trial may have to comply with different requirements.

For the purposes of this section, "original study documents" are defined as:

- Subject medical records created at or available to the enrolling center during the subject's participation in the trial, or any other document that supports entries in the EDC system and represents the original source of that information, including but not limited to applicable sections of medical charts, patient correspondence, laboratory data, pharmacy logs and drug accountability forms, as well as any forms or documents used to compile or maintain original subject data or study procedural information. Intermediary documents and worksheets used to organize and compile original records into a form that facilitates easier transcription into the EDC do not represent original study documents. Certain data may be entered directly into the EDC in which case the EDC system represents the original study document.

- All Essential Regulatory Documents (as defined under Good Clinical Practice Regulations) including: all material communications with the IRB; all communications with the sponsor (including the surgical center, reading center, outcomes committee, endpoint committee, safety monitor, Emissary's monitoring staff, etc.) that are related to study subjects or which otherwise document material study-related procedures or safety issues; and, all training records and documentation that all participating staff are suitably qualified and authorized (CVs, 1572, Delegation Log, etc.).

- Archival copies of the data and electronic documents from the VISION-EDC system.

All study documents should be uploaded to the Electronic Trial Master File (eTMF) section of the VISION-EDC system. VISION will be used as the master repository for all site and sponsor regulatory documents, and all patient source documents with the exception of DICOMs and any records not uploaded to the EDC (perhaps for confidentiality reasons or due to specific site discretion, such as might be suitable for financial contracts), sites generally do not need to maintain duplicate local files unless otherwise mandated by local institutional requirements.

At the conclusion of the study, all entered patient data and uploaded documents (with the exception of Modified Rankin videos and DICOMs) in the VISION-EDC system will be archived and provided to the site on DVDs. Modified Rankin video interviews uploaded to the Glasgow outcomes center will be archived for a period of 3 years after study database lock Individual study centers are not required to maintain a copy of the images after upload with the documented score itself and not the video serving as the source data. Due to their extreme size, DICOMs submitted to the EDC system will not be maintained long-term in the EDC system, but rather will be promptly deleted once they have been reviewed by the reading and surgical centers. Sites will be responsible for retaining DICOMs via their local PACS system (or local copies of CDs).

Regulations require that study documents (including the archive CDs and any study documents not uploaded to the EDC) must be retained in the files of the responsible investigator for potential review by regulatory agencies. As this is an international study conducted under the jurisdiction of multiple regulatory bodies (FDA, NIH, Health Canada, ICH, etc.) and for not in support of any one specific regulatory application, retention requirements may be considerably longer than what may be required under local or regional regulations or other trials being conducted at the site. As such, the principal investigator must retain the study documents until otherwise instructed by the coordinating center. The expected retention period is a minimum of 2 years after the final report is submitted to the FDA after the conclusion of the overall clinical trial, irrespective of any particular site's participation.

11.10.2. Direct Access to Source Data/Documents

Investigator/Institution will permit trial-related monitoring, audits, IRB/EC review, and regulatory inspections by providing direct access to source data and documents.

11.10.3. Role of Data Management

Regulatory Compliance. The administrative and clinical aspects of the study will be conducted to ensure compliance with the protocol and Title 21 of the United States Code of Federal Regulations

(CFR) Good Clinical Practices (GCP) and International Conference on Harmonization (ICH) GCP Guideline E6, Section 5 as well as local applicable regulatory requirements.

Source Data. All data related to the initial and subsequent IVC placement procedures, the reading of all image scans, and all follow-up visits may be recorded directly onto the electronic CRF and considered source data. All test article administrations will be recorded in the patient's permanent medical record and on the electronic CRF.

Quality Control and Management of Data. The CC will prepare reports summarizing patient selection and protocol adherence as well as data quality. At the patient closeout, the BC will develop and manage data analyses that summarize the study's findings. The CC will prepare the final reports summarizing the overall performance of all sites with respect to the protocol and the quality of the data generated. Each performance center must demonstrate that it is properly staffed and equipped to support the data management activities.

Data forms associate directly to an electronic database. Before the trial begins, the CC and sites will have approved consent forms and IRB approvals, fully executed contracts and agreements, curriculum vitae for the principal investigator listed on the FDA 1572 form, and normal lab ranges for the local labs. Site performance as well as detailed eligibility and exclusion criteria and reports will be generated with graphic representation of the trial's progress monthly. Subject eligibility logs will be updated daily (via entry of screen failures and randomized patients in the eCRF) by each study center. During monitoring, case report forms will be compared to source documentation to check for accuracy and completeness. Also, the QA Monitor will crosscheck all forms against each other for reporting accuracy. All discrepancies will be reported to individual sites by the QA Monitor using the electronic query system within the eCRF. Sites will be required to make the necessary changes/clarifications within the EDC system.

Each patient is assigned a unique study number. A list of patient names and any identifying information will be kept in a separate offline document to ensure patient confidentiality. Daily data collection of ICP management, ICU care, catheter monitoring, neuroimaging, and NIHSS scores will assess the patient's clinical response to treatment as part of the clinical trial. These data will be used to assess compliance with stopping rules and care directed at independence. The results of daily coagulation studies also will be collected. The modified Rankin, EQ-5D, and Barthel Index scales are used to assess clinical outcome at one, three, six, nine, and 12 months. In addition the NIHSS, extended Glasgow Coma Scale, Stroke Impact Scale, Mini-Mental and video-taped modified Rankin Scale will also be used at 1, 6, and 12 month visits only as the procedures for collection preclude the use of the telephone at the 3 and 9 month follow-up visits. A CT scan will be done at the 1 and 12 month clinic visit. Data collection forms are completed daily via the web-based eCRF. CD ROM disks containing CT studies in DICOMM format are sent to the Central Reading Center at JHU no more than 14 days after enrollment (or alternatively the CT electronic files may be uploaded to the eCRF system if such capability is available). Remaining follow-up data collection forms and any additional CT scans, including the follow-up CT scans, will be sent to the CC no more than 7 days following the last follow-up visit. A paper bedside worksheet source document binder may be prepared locally to further document the existence of the subject and substantiate the data collected. An examiner blinded to treatment assignment will obtain the follow-up clinical data at 1, 3, 6, 9 and 12 months post-stroke.

Data will be entered directly into an electronic data collection system (VISION EDC, Prelude Dynamics Inc., Austin, Texas) onto preformatted fields. Data may first be entered onto parallel paper bedside worksheets and then subsequently transcribed to the eCRF, according to the investigator and coordinator's preferences. Access to electronic CRFs will be via secure login. All changes to the data in the EDC will be date- and user-stamped and tracked in a secure, non-editable audit trail in accordance with FDA and ICH requirements pertaining to electronic systems used in clinical trials (e.g. FDA 21-CFR-11).

Form designs and field-level edit checks will be defined by Emissary International LLC (Austin, TX) and reviewed by the CC according to the protocol and specifications. These checks will include missing data warnings as well as out of expected range warnings. The eCRF system will be hosted from a database server located in an access-controlled tier-1 data center, protected by multiple T1 connections, battery, and generator backups, and redundant climate controls. The file server will be backed up daily and a backup facility is available to quickly assume hosting responsibility in the event of a catastrophic loss of the original hosting center.

Upon data receipt, the QA Monitor will remotely monitor the available data and compare it to source documentation.. The QA Monitor will query the site coordinator and generate data queries within the EDC system. After queries are addressed by the investigator/coordinator, the QA Monitor will review to ensure proper correction and resolution.

The BC will perform statistical analyses using Stata (StataCorp, TX) upon transfer from XML. Key variables will be printed and compared to the original notations in the patient's medical record to ensure accuracy of data collection.

Data Collection and Reporting. Data for each patient will be reported and recorded on electronic case report forms (eCRF). Case report forms must be completed for every enrolled patient. This means all patients who have a signed informed consent, undergo screening procedures, fulfill all eligibility criteria, and are randomized.

Electronic audit trails will track all changes to the eCRF. If any entry requires a change, all previous entries are retained and may be displayed as part of the audit trail. Date/time stamps track each change.

All time fields throughout the forms are in military time format. All date fields throughout the forms are day-month-year format.

Biostatistical Center Data Management Responsibilities. The BC will assist the CC with the data collection systems and instruments, data management oversight and quality assurance, statistical analysis and data interpretation, designation of appropriate methods used for statistical analysis of the data, and professional and scientific report writing.

Coordinating Center Activities. Data analysis is approved by the Executive Committee to take place at The Johns Hopkins University Department of Biostatistics (Biostatistical Center). Full analysis will occur when the data has been cleaned and the database locked. The BC will be partially unblinded as to

A/B treatment allocation so that analysis according to treatment effect can occur. The EC will remain blinded to treatment allocation. The results of all blinded data analyses will be given first to the EC. Initial access to this information will be via its EC representative(s) so that early and inappropriate access to this information may be avoided. Futility analyses will not be conducted. Stopping rules have been established on safety and efficacy.

Dosing stopping rules include:

1. IVC is discontinued
2. 12 doses are given
3. Radiographic evidence of return of CSF flow in both the 3rd and 4th ventricles
4. Estimated 80% of clot lysis is accomplished in ipsilesional ventricle with a 2nd catheter and IVH related mass effect is treated
5. Symptomatic, significant bleeding event (local or systemic)
6. In the opinion of the investigator an event is deemed test article related and the nature, intensity, or severity of that event makes further dosing unsafe or imprudent.

Trial stopping rules include:

1. Death (occurring $\leq$ 30 days post symptom onset) $\geq$ 40%
2. Bacterial ventriculitis, bacterial meningitis incidence (occurring $\leq$ 72 hours post last dose) > 20%
3. Rate of symptomatic bleeding events (occurring $\leq$ 72 hours post last dose) > 25%

Crude data will be held at the Coordinating Center. Collations of this data will be supplied to the safety monitoring committee by the BC at pre-determined times requested by the DSMB, or at any other time the committee may so determine.

The Coordinating Center, based at JHU, has been developed for data collection, quality control, and to assist in safety monitoring. The CC will be supervised by the Study Chairman and consist of a project administrator, a data research assistant, the safety officer, and a data analyst/manager. The CC's primary function is to collect data from the site clinical investigators as well as from the central CT readers, to ensure accuracy and completeness of data collection, to manage, edit and clean the data that have been entered into an electronic database designed for the study, and produce periodic data summaries for the Study Chairman and safety monitors. The CC will also be responsible for management of regulatory documentation, protocol compliance and budgetary issues. An outline of data flow in this study is provided below.

11.10.4. Quality Assurance

The Surgical Center. The Surgical Center develops and maintains standards for the placement and subsequent surgical management of intraventricular catheters (IVCs). The Surgical Center is located at NorthShore University HealthSystem, Evanston, IL. The surgical center monitors IVC placement, maintenance, clot removal assessments, catheter discontinuation protocols, and evaluates the safety and efficacy of the surgical procedure. The center ensures uniform, ongoing utilization and application of surgical care throughout the intervention time period. It will participate in subject and site evaluation of surgical results, such as: accuracy of catheter placement, complications of catheter placement, catheter-

related ICP management, and relation of catheter placement to clot removal. The Center participates in the overall evaluation of the medical results of the surgical treatment. Protocols include IVC placement and maintenance, clot removal assessments, and catheter discontinuation. Analysis is intended to evaluate the safety and efficacy of the surgical procedure. The Surgical Center is supported by a Surgical Committee. The Surgical Center is available on an emergency basis to trial surgeons regarding protocol clarifications and as a reference for any trial Committee. The Surgical Center has produced IVC Procedure tutorials that are available on line. All investigators are required to view the tutorial and complete a posttest. The Surgical Center manages the Surgical Committee which meets quarterly.

Outcomes Center. The University of Glasgow, in collaboration with several universities internationally, has created a database from 21 clinical trials over the past 16 years amassing over 15,000 subjects. Outcome measures using the Modified Rankin Scale will be analyzed at the VISTA Centre. The VISTA Modified Rankin training program is used to train and certify study investigators and coordinators to asses the mRS scores of subjects enrolled into the trial. Dr. Kennedy Lees and his coworkers at the University of Glasgow will conduct a full analysis of outcome data and assist the Biostatistics Center complete the final trial analysis.

Quality Control and Quality Assurance. The Principal Investigators at The Johns Hopkins University and the Coordinating Center personnel involved in the clinical research have a good track record of cooperation with experienced stroke investigators. The organizational structure of the trial contains an Executive Committee, Medical Safety Monitor, and Data and Safety Monitoring Board (DSMB).

The Executive Committee consists of six site principal investigators, the Study Chairman, the independent medical safety monitor, the independent Chairman of the DSMB, and the trial's biostatistician. The Chairman of the committee is selected by mutual consent of the site study investigators. The EC is responsible for the selection of the sites and investigators.

The Medical Safety Monitor is independent of the Coordinating Center and experienced in the field of clinical stroke trial conduct and stroke therapies. The Executive Committee and the Medical Safety Monitor have determined appropriate data flow and stopping rules. Recommendations from the Medical Safety Monitor will be made to the DSMB concerning clinical data and safety analyses regarding continuation or cessation of the trial. The Executive Committee will make the final decision concerning the status of the trial. The Executive Committee has the right to govern the activities of the Coordinating Center. The Medical Safety Monitor will also review the clinical history of all patients with SAEs. He will provide his interpretation of relationship of each SAE to the study intervention for the DSMB. The DSMB will provide all pre-planned data reviews and be available for any emergent reviews.

The Trial Pharmacist, located in the JHU Department of Pharmacy will serve as the central Randomization Center and will be the only project team member with access to the blinded computer-generated randomization code (drug or placebo) across all sites. Individual site pharmacists will have knowledge of the randomization code for their patients, as received from the EDC system at the time of randomization.

Training and Communication. Investigator meetings for this protocol will take place in Baltimore, MD and at other locations for study center personnel who are not able to conveniently travel to

Baltimore. Some meetings will take place via webinar. Study personnel from the Johns Hopkins University Coordinating Center will meet with 75 investigator-coordinator teams. The meeting is expected to last one and one-half days. Overhead images and slides will be presented during the start-up meeting. The visual aids provided to each site will include slides on background and significance, Good Clinical Practices, investigator responsibilities, FDA requirements, surgical protocols, case report forms (eCRF), and other specifics of the protocol. This site initiation process will acquaint the center personnel with the design and methods of the trial, the study organization, treatment monitoring, and integrity of data collection.

We will instruct the coordinators on the use of the VISION EDC system used to capture study data, and on the relevant regulatory requirements. Formal certification will be required of each site investigator who will be administering study drug. NIH Stroke Scale and modified Rankin Scale certification will be required of all site study team members who will assess this patient outcome. Human Subjects training is also required of each study site team member.

Study Monitoring. Study monitors will periodically review performance characteristics of the trial as it proceeds from design and development through its completion. The performance monitoring will emphasize the importance of data collection, quality data, and protocol adherence. Appropriate findings will be reviewed by the trial leadership and used to take corrective actions when appropriate.

Study monitoring will include an assessment of each site's performance in protocol adherence, patient recruitment, thorough follow-up, and error-free reporting. Site visits will be made selectively to participating study centers for the purpose of assessing its performance or its potential for performance on an as-needed basis. A site visit will consist of a private meeting of the site visitor(s) with the key investigator and members of the clinical research staff, including neurosurgery personnel and CT staff and support personnel. There will be an inspection of the treatment and care areas and record storage facilities to assure patient safety and confidentiality. It is not expected that every site will require onsite monitoring visits. Alternatively, remote monitoring will verify the accuracy and completeness of data in the VISION EDC system, the existence of applicable FDA or other regulatory files and requirements, and that the investigator's obligations are being fulfilled. Remote monitoring will occur after every patient completes the acute treatment phase. Data will be tracked from source documents to the electronic data file to confirm accuracy. Secure passwords restricting network and local access to the electronic data file will be reviewed.

Radiographic Masking. Although determinations for routine patient care will be performed locally, radiographic determination needed for treatment comparisons will be made in a central radiological setting and be part of the permanent data files. Centralizing the CT scan interpretations ensures that the required masks are maintained. Central reading will assure a high degree of uniformity and standardization of the measurement of the hemorrhage size and assessment of edema and mass effect. The RC will be blinded to clinical information, such as the response of the patient to test article. All imaging studies will be catalogued and analyzed, and the results entered into a separate section of the EDC system.

11.10.5. Adverse Experience Reporting

In the event of an adverse event, the first concern will be for the safety of the subject. For all adverse events, investigators are required to record relevant data on source documents and the eCRF and to report these data to the Coordinating Center. All adverse events, serious or otherwise occurring after presentation to the emergency department but prior to the initiation of test article will be documented on the Concurrent Conditions/Procedures screen in the EDC system. All adverse events and serious adverse events that occur during the acute treatment phase (ending at day 7) will be recorded on the Medical Event form along with all neurological AEs and all SAES that occur through the day 365 follow-up visit. This will allow for reporting of all adverse events in each of the three distinct time periods and for quick assessment of any temporally-related events (i.e., those events occurring in the acute treatment period). Follow-up assessments must be repeated to document return of any abnormalities to normal, or to document other outcomes of any adverse events. The investigator must follow adverse events to resolution whenever possible. Definitions, serious criteria, and guidance for reporting follow.

For patients who are randomized but have either an obstructed flow pathway or where catheter patency cannot be established, safety data (AEs/SAEs) will be collected through day 7. Final outcome of all events at day 365 are to be recorded if not recorded earlier. All randomized patients receiving at least one dose of test article will be included in intent-to-treat analyses.

Adverse Event Definition. An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease, syndrome, or intercurrent illness in a subject who receives test article (or was intended to receive test article) that emerges during test article administration or is a preexisting condition that worsens relative to the pretreatment state, and that does not necessarily have a causal relationship to this treatment. Note: Unchanged, chronic conditions should not be recorded as an adverse event unless there is an exacerbation of the chronic condition.

Adverse events will be reported and recorded on the electronic case report forms defined by their duration (start/stop) and classified as their intensity using grades 1 through 5 with grade 1 being mild and grade 5 being death.

Serious Adverse Event Criteria. Serious adverse events (SAE) are adverse events which result in any of the following outcomes. For purposes of this study, regulatory agency reporting responsibilities have been designated to the Coordinating Center.

1. It resulted in **death** (i.e., the adverse event caused or led to death) whether or not attributable to test article.

2. It was **life-threatening** (i.e., the adverse event placed the patient at immediate risk of death; it does not apply to an adverse event that hypothetically might have caused death if it were more severe).

3. It required or prolonged inpatient **hospitalization** (i.e., the adverse event required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not serious adverse events by this criteria).

4. It was **disabling/incapacitating** (i.e., the adverse event resulted in a substantial disruption of the patient's ability to carry out normal life functions).

5. It does not meet the above criteria but in the opinion of the investigator or medical monitor **may jeopardize the patient or may require medical or surgical intervention** to prevent one or more of the outcomes listed above.

Guidance for Reporting. Any alarming, serious, or unexpected adverse event, including death due to any cause, which occurs during this study, inclusive of the follow up period (day 365), and whether or not thought to be related to the administration of test article, must be reported immediately (within 24 hours of learning of the event) to the Coordinating Center. The CC will then notify the Study Chairman, Genentech, Inc., the Medical Safety Monitor, the ICU Complications Monitor, Health Canada, the UK and European QA Monitors, and the FDA. The UK and European QA Monitors will notify the MHRA and Competent Authorities in all other Member States concerned as well as to the Ethics Committees concerned as necessary.

Name	Title	Phone Number	Fax Number	Email Address
24-hour pager	Coordinating Center	410-283-8342	410-502-7869	
Daniel F. Hanley, MD	Principal Investigator	410-614-6996 Cell: 410-615-3749	410-502-7869	dhanley@jhmi.edu
Genentech Drug Safety	Genentech, Inc.	800-835-2555	650-225-4682 or 650-225-5288	
Pat Reilly, RN, MSN	Sr. Medical Science Liaison, Vascular Medicine (Genentech)	717-566-7993	717-566-7994	patr@gene.com
FDA fax number for IND Safety Reports	FDA		1 (800) FDA-0178	
J. Ricardo Carhuapoma, MD	ICU Safety Monitor	410-955-7481	410-614-7903	jcarhua1@jhmi.edu
Carlos S. Kase, MD	Medical Safety Monitor	617-638-5102	617-638-7758	cskase@bu.edu
Ken Butcher	Health Canada	780-407-2171	780-407-1325	ken.butcher@ualberta.ca
Barbara Gregson, PhD	QA Monitor, UK; MHRA	+44 191 233 6161 ext. 22175	+44 191 256 3268	barbara.gregson@ncl.ac.uk
Alan Cohen	QA Monitor, Europe	+32 4 738 650 91		alanscohen@skynet.be
Vandna Kishore	FDA/CBER (IND File)	301-796-4193	301-796-9842	Vandna.Kishore@fda.hhs.gov

Methods for Eliciting, Recording and Assessing Adverse Events

Eliciting Adverse Events. To elicit adverse events, simple questions with minimal connotations should be used as the initial questions at all evaluation points during the study. For example:

- How have you felt since your last visit?
- Have you had any health problems since you were here last?
- Have you (or the patient) had any serious bleeding? Examples of this include blood transfusions, a sudden drop in blood pressure, blood in urine or stool, coughing or vomiting blood or any other internal or external bleeding.

- Have you (or the patient) suffered bleeding on the brain, a stroke, or any other change in function of the brain or nerves?
- Have you (or the patient) had any symptoms such as sudden onset of shortness of breath, coughing up blood, purple discoloration of the feet, loss of pulse in legs or feet or other problems with blood clots?
- Have you had any unusual or unexpected worsening of your underlying medical condition?
- Have you been hospitalized since the last follow-up visit? If yes, was it for placement of a ventriculoperitoneal shunt?

Recording Adverse Events. When completing a SAE Report form, investigators should consider the following when assigning a primary event code from the adverse event coding guide:

- Whenever possible, use recognized medical terms when coding and recording adverse events on the Medical Event and SAE Report forms in the eCRF. Do not use colloquialisms and/or abbreviations.
- If known, code and record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms on the Medical Events and SAE Report forms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be coded and recorded as individual adverse events on the serious adverse event form (e.g., if congestive heart failure and gastrointestinal bleeding are observed at the same time, each event should be coded and recorded as an individual adverse event).
- Adverse events occurring secondary to, or as an outcome of, other events (e.g., sequelae) should be identified by the primary cause. A "primary" adverse event, if clearly identifiable, generally represents the most accurate clinical term to code and record on the Medical Event and SAE Report forms in the eCRF. Events occurring secondary to the primary event should be described in the narrative description of the case. For example:

Orthostatic hypotension	→	Fainting and fall to floor	→	Head trauma	→	Neck pain

The primary adverse event is **orthostatic hypotension**.

Assessing Causality (Attributability of Serious Adverse Events to test article): The investigator and/or Medical Monitor will determine which events are associated with the use of test article. For reporting purposes, an AE should be described as UNRELATED, POSSIBLE, PROBABLE, OR DEFINITELY RELATED association to test article, according to the following definitions:

- Unrelated: There is evidence that the adverse event definitely has an etiology other than the test article. AEs with onset more than 72 hours post test article administration are not expected to be related to the test article.

- Possibly Related: The adverse event has a temporal and/or biological relationship to test article administration. However, an alternative etiology may be responsible for the adverse event.

- Probably Related: The adverse event has a temporal and/or biological relationship to test article administration. The event is unlikely to be related to an alternative etiology. There is a reasonable response on interruption/withdrawal of test article administrations (dechallenge). Rechallenge information is not required.

- Related: The adverse event has a temporal relationship to test article administration and resolves when test article is discontinued. An alternative etiology is not apparent.

Treatment Discontinuation. If a subject is discontinued from test article administrations for any reason, study site personnel must clearly report and document the circumstances and data leading to any discontinuation using the case report forms. It must be determined if the reason for stopping test article administration is an adverse event, for example, symptomatic bleeding associated with drug administration. Adverse events that required discontinuation of dosing or withdrawal of the subject from follow-up should be treated as a medical event of interest (MEOI) and detailed on the SAE form in the eCRF.

SAE Report eCRF Completion Methods: In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the narrative of the SAE Report form:

- Identification and coding of the primary event term
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to test article
- If a death occurred, autopsy results if available

SAE Report eCRF Follow-up Information Methods. Additional information may be added to a previously submitted report by any of the following methods:

- Add to original SAE Report eCRF
- Add documents and submit as follow-up with the original SAE Report eCRF

Occasionally the CC may contact the investigator for additional information, clarification or current status of the subject for whom an adverse event was reported.

For questions regarding SAE reporting, you may contact the CC noted in above under Guidance for Reporting.

General Reporting of Serious Adverse Events Associated with Test Article.

An expedited IND safety report will be used to notify the FDA IND division of each serious unexpected suspected adverse reactions according to FDA regulations, part 312 and Guidance for Industry and Investigators: Safety Reporting Requirements for INDS and BA/BE Studies effective March 28, 2011. In accordance with these regulations, this protocol has a pre-specified monitoring plan for determining if subjects receiving the intervention are at higher risk for mortality and will only report a death as an

expedited IND safety report if there is evidence of a causal relationship between the intervention and/or the study drug and the event resulting in death. In addition, an expedited IND safety report will be used to notify the FDA if there is an imbalance between the arms suggesting there is a reasonable possibility that the intervention or the study drug caused any of the safety endpoints: symptomatic bleeding, cerebral infection, mortality occurring with seven days of the surgical intervention, 30-day mortality. Otherwise, the occurrence of these safety endpoints will be reported on an annual basis.

The CC will report all AEs and SAEs to the Study Chairman as the IND Sponsor (in accordance with CFR 312.32: IND Safety Reports) and the DSMB either immediately or as a routine summary report depending upon the severity of the event.

Any study report submitted to the FDA by the Sponsor-Investigator will be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report).

The CC will submit events meeting the following criteria to the Food and Drug Administration (FDA) as expedited IND Safety Reports, Genentech Drug Safety using the fax cover sheet in Appendix 5 and to the UK and European QA Monitors according to the guidance and timelines below. The completed Medwatch/case report will be faxed immediately upon completion to the FDA and Genentech Drug Safety. The FDA fax number for IND Safety Reports is 1 (800) FDA 0178. All written IND Safety Reports submitted to the FDA by the Investigator will also be faxed to Genentech Drug Safety at (650) 225-4682 or (650) 225-5288. For questions related to safety reporting, please contact the CCC or Genentech Drug Safety by telephone at (888) 835-2555 or by Fax at (650) 225-4682 or (650) 225-5288.

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the CCC or the Genentech Drug Safety representative noted above or the Medical Science Liaison assigned to the study (see table above). Relevant follow-up information should be submitted to the CCC for distribution to the FDA, Health Canada, Genentech Drug Safety, the UK and European QA Monitors, and all participating investigators as soon as it becomes available and/or upon request.

> **7 Calendar Day Telephone or Fax Report:** The CC will notify the FDA, Health Canada, Genentech, the UK and European QA Monitors, and all participating investigators for local IRB/Ethics Committee review of any **fatal or life-threatening** adverse event that is **unexpected** and assessed by the investigator to be **possibly, probably, or definitely related** to the use of test article. Unexpected adverse events are any event in which the specificity or severity is not consistent with the natural history or ICH or IVH without test article administration. Unexpected will be defined as the nature, specificity, or severity of an event that is not consistent with the risk information described in this protocol, the Alteplase package insert (PI), or investigator's brochure (IB). Such reports will be telephoned or faxed to the FDA, Health Canada, the MRC, and Genentech within 7 calendar days of the CC first learning of the event. The UK and European QA Monitors will submit the reports to the MHRA and Competent Authorities in all other Member States concerned as well as to the Ethics Committees concerned as necessary. Relevant follow-up information will be submitted to all parties as soon as it becomes available.

15 Calendar Day Written Report: The CC will notify the FDA, Health Canada, Genentech, the UK and European QA Monitors, and all participating investigators for local IRB/Ethics Committee review, in a written IND Safety Report, of any **serious, unexpected** AE that is considered **possibly, probably, or definitely related** to the use of test article. An **unexpected** adverse event is one that is not already described in this protocol, the Alteplase PI, or IB. The UK and European QA Monitors will submit the reports to the MHRA and Competent Authorities in all other Member States concerned as well as to the Ethics Committees concerned as necessary. Relevant follow-up information will be submitted to all parties as soon as it becomes available.

15 Calendar Day Written Report: The CC will notify Genentech Drug Safety within fifteen (15) calendar days of the Awareness Date all SAE reports that are related to the rt-PA and AEs of Special Interest (regardless of causality).

30 Calendar Day Written Report: The CC will notify Genentech within thirty (30) calendar days of the Awareness Date all SAE reports that are unrelated to the rt-PA administration(s) and any reports of pregnancy following the start of administration of rt-PA.

Quarterly Written Report: The CC will notify Genentech of all non-serious AEs originating from the study.

Annual Written Report: The Data Management Center will notify the FDA, Genentech, and the European Member States in whose territory the clinical trial is being conducted and the Ethics Committees concerned as necessary with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety. Each Member State shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in a European database to which, in accordance with Article 11(1), only the Competent Authorities of the Member States, the Agency and the Commission shall have access. The Agency shall make the information notified by the sponsor available to the Competent Authorities of the Member States.

• Written IND Safety reports will include an **Analysis of Similar Events** in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events will be analyzed and the significance of the new report in light of the previous, similar reports commented on.

• Written IND safety reports with Analysis of Similar Events will be submitted to the FDA, Health Canada, the MRC, Genentech and all participating investigators for local IRB/Ethics Committee review within 15 calendar days of the CC first learning of the event. The UK and European QA Monitors will submit these reports to the MHRA and Competent Authorities in all other Member States concerned as well as to the Ethics Committees concerned as necessary.

For questions related to safety reporting, please contact the CC.

11.11. Human Subjects

11.11.1. Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki (October 2008) or any subsequent official revision thereof.

11.11.2. Ethical/Institutional Review Board

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB/EC for review and must be approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB/EC requirements.

The Principal Investigator is responsible for keeping the IRB/EC appraised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB/EC must be updated at least once a year. The Principal Investigator must also keep the IRB/EC informed of any significant adverse events.

Investigators are usually required to promptly notify their respective IRB/EC of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the investigator. Some IRBs or ECs may have other specific adverse event requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB/EC any written safety report or update provided by the CC (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

The site investigator will provide the CC with documentation of institutional review board approval of the protocol and the informed consent document before the study may begin at the site. The ethical review board(s) will review the protocol as required.

The Investigator is to supply the following to the study site's institutional review board(s):

1. The current clinical investigator brochure (Genentech, Inc., San Francisco, CA)
2. The current protocol and informed consent document
3. All updates to the clinical investigator brochure during the course of the study
4. Human Subjects Training Certification
5. Any specific information the review board requires.

The Investigator must provide the following documentation to the CC:

1. The institutional review board's initial and annual re-approval of the protocol.
2. The institutional review board's approvals of any revisions of the informed consent document or amendments to the protocol or informed consent.

11.11.3. Conflict of Interest

Individuals who are aware of a potential or existing conflict of interest that may preclude them from committee involvement or investigator participation will disclose all potential conflicts to the EC.

Dr. Daniel F. Hanley (Study Chairman and holder of the IND) has formally removed himself from any personal interest in the Johns Hopkins University use patent for rt-PA.

11.11.4. Informed Consent

The informed consent document will be used to explain the risks and benefits in simple terms to the patient or authorized representative before the patient is entered into the study. The informed consent document must contain a statement that the consent is freely given, that the patient/authorized representative is aware of the risks and benefits of entering the study and the patient is free to withdraw from the study at any time. A sample informed consent form is included in Appendix 3.

The Investigator is responsible for obtaining informed consent from each patient or their authorized representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug. Informed consent by an authorized representative of the patient should be obtained according to the clinical judgment of the investigator.

11.11.5. Subject Confidentiality

All computer entry and networking programs will be done using Study Identification Numbers (SIDs) only. The consent form states that source documentation, such as medical records, and radiographic images will remain identified but will only be shared with those entities involved in the trial and disclosed in the consent form. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee.

11.11.6. Data Disclosure

All information concerning the basic scientific data and information supplied by the investigator and not previously published are considered confidential. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the study's Executive Committee written consent. Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. The Investigators understand that the information developed in this clinical study will be used by the trial Investigators in connection with the development of this protocol and therefore, may be disclosed as required to other clinical investigators, to the United States Food and Drug Administration, and to other U.S. and non-U.S. government agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the U.S. FDA and NIH with complete test results and all data developed in the study. Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, the drug manufacturer and the IRB/EC for each study site, if appropriate.

11.11.7. Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the NINDS, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

11.11.8. Human Subjects Research Training

Education in the protection of human research participants has been met by certified completion of the Johns Hopkins University School of Medicine Web-based Research Compliance course, "Human Subjects Research Training" by all relevant Key Personnel. The course consists of the University of Minnesota Web modules on Informed Consent, the Consent Process, and After Informed Consent, a Johns Hopkins University School of Medicine Module on local IRB requirements, and achievement of a passing score on the Knowledge Assessment module.

Education in the protection of human research participants will be met by certified completion of the "Human Subjects Research Training" by all relevant site investigators and coordinators at each participating site. The course must be equivalent to the University of Minnesota Web modules on Informed Consent, the Consent Process, After Informed Consent, Module on local IRB requirements, and participants must achieve a passing score on the Knowledge Assessment module.

11.11.9. Investigator Responsibilities

Each site investigator affirms that he or she is qualified by education, training & experience; thoroughly familiar with rt-PA and its use, and aware of and in compliance with Good Clinical Practice (GCP/ICP). The investigative team agrees to permit monitoring and auditing and maintain a current co-investigator list and information on delegated authority.

Investigator responsibilities include being able to recruit required number of subjects; having time to conduct and complete the trial; having an adequate number of qualified staff and facilities for the safe and proper conduct of the trial. The investigator must ensure that all persons assisting with the trial know the protocol and trial functions. The principal investigator agrees to make all trial-related medical decisions, to ensure medical care for adverse events including clinically significant labs, to inform the subject's primary physician of the subject's participation in the trial, and to ascertain the reason(s), if subject withdraws prematurely from the trial. The investigator further agrees to obtain IRB approval, and provide documents to the local IRB during the trial.

The investigator agrees to conduct the trial in compliance with the protocol, not to implement any deviation without CC agreement, document and explain any deviation from the accepted protocol, account for use of rt-PA on site, and follow the trial's randomization procedures. The investigator will be responsible for his or her investigative team members as they obtain and document informed consent; ensure the accuracy, completeness, legibility, and timeliness of data; maintain source documents; change or correct edited data; maintain trial documents; and report all serious adverse events. The Principal Investigator agrees to record all temporally-related adverse events, and inform the institution of trial completion and final reports

11.12. Publication of Research Findings

11.12.1. Publication Policy

The results of the trial will be published regardless of its outcome. Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee and enforced by the Publication Committee. Publication regarding further analyses performed on the data will be by mutual agreement between the Executive Committee and the site investigators.

The investigator may publish or present at scientific meetings the results of this study, provided that confidential information is not disclosed, and only after obtaining advance written consent from the Executive Committee. Consent may be withheld at the sole discretion of Executive Committee.

In this regard, a copy of all public disclosures, including but not limited to publication manuscripts, abstracts, and seminar presentations, should be provided to the Executive Committee for review, at least 30 days before the manuscript is submitted to the publisher or a presentation is made.

The Executive Committee agrees that before it publishes any results of the study, a pre-publication manuscript will be provided to the investigator for review at least 30 days before being submitted to a publisher.

Additionally, the Clinical Study Report (final study report) and any literature articles that are a result of the study should be sent to Genentech. Copies of such reports will be faxed to the assigned Clinical Operations Contact for the study: Lytics IST central mailbox: lytics-gsur@gene.com or fax: 866-283-2263.

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Appendix 1: Rationale for 1.0 mg Dose Selection

1. Preliminary Studies Performed by Investigators

a. C.1 Literature Produced by PI & Investigative Group

b. C.2Background: Animal Model and early Human data

c. C.3. Investigator Data Supporting Treatment of IVH

2. Surgical Guidance: Report of CLEAR IVH Surgical Review Committee – dated 09/19/2006

3. Safety Trial Analyses & Results – dated 12/13/2003

4. Overview of CLEAR IVH Part A – dated 06/20/2005

5. Stage 2: Dose Tier 1 Results – dated 07/28/2006

Appendix 1: Rationale for 1.0 mg Dose Selection

Preliminary Studies Performed by the Investigators

C.1.1. Proof of concept: Animal data. Pang et al. developed a model of IVH and intraventricular thrombolysis in which clotted blood was injected into the ventricles of adult dogs.[1-3] They determined 10,000 IU as the minimal dose of urokinase (UK) required to lyse, *in vitro*, 10 mL of clotted canine blood, they then doubled the dose and tested for safety *in vivo* by injecting 20,000 IU every 12 h for 4 days into the ventricles of six adult dogs through an implanted ventricular catheter.[1, 3] Rapid clearance of intraventricular blood occurred in the treated versus the control animals. With UK treatment all blood was removed before 1 week, mainly in the initial 2 to 3 days.[1] There were no intracranial or systemic hemorrhages and no chronic changes in the brain or meninges on histology sections at 3 months. In a pig model, Mayfrank showed prolonged ventricular dilatation and an association of blood clot volume with mass effect.[4] Significant decline in this mass effect was noted at 1.5 h and 7 days when rt-PA was used for intraventricular thrombolysis. Importantly, in both canine and porcine models, the greater the volume of blood clot injected into the ventricles the greater the likelihood of animal death.[2, 4]

C.1.1.1. Effect of clot treatments on neurologic function. In Pang's model, there is a direct effect of reduction of rapid clot size on a predefined canine consciousness score in the UK-treated dogs compared to untreated control dogs. When return-to-normal consciousness levels were assessed, the treated group regained consciousness in 3 days vs. 10 days in the control group. When clot resolution rates are compared, early return of normal consciousness and more rapid removal of clot appear to be treatment-specific effects in this model.[1-3]

This controlled study then compared the rate of IVH resolution between 10 untreated control dogs and 10 dogs treated with the regimen above.[1] In the untreated dogs, complete lysis of the intraventricular blood clot required 38 to 65 days. Eight dogs developed hydrocephalus and had extensive ependymal and subependymal damage of the ventricular walls on histology section. In the treated dogs, the intraventricular blood clot was completely lysed in 3 to 6 days (SD = 5.2 $\pm$ 1.2) with no intracranial or systemic hemorrhages. The treated dogs promptly recovered neurological function, and only two developed hydrocephalus. Histology sections revealed no ventricular wall damage. Thus, in a canine model, Pang and co-workers demonstrated conclusively that intraventricular thrombolysis significantly hastened resolution of the intraventricular blood clot, promoted rapid return of consciousness within 3 days, decreased the degree and incidence of delayed communicating hydrocephalus, and improved neurological outcome.[1, 2]

C.1.2. Proof of concept: Human data. A Cochrane review of the safety and efficacy of thrombolysis is available (Haines and Lapointe). Pilot series experience with thrombolysis is as follows. In seven independent studies, the use of intraventricular thrombolytic agents has been reported in 74 patients with ICH or SAH.[5-11] Seventeen patients were treated with UK (12,000 - 96,000 IU/day) and 57 with rt-PA (4 - 20 mg/day). Good neurological outcome was reported in 50 of the 74 patients as measured by each group's criteria; 22 of the 74 had long term follow-up, and of those, 8 developed delayed communicating hydrocephalus requiring permanent CSF diversion. Complications potentially attributable to treatment or extraventricular drainage (EVD) included five cases of bacterial meningitis, one increase in hematoma volume[5],and two extradural hematomas.[12] This safety information suggests an acceptable side-effect profile for low-dose thrombolytic treatment, but also signals the need for prospective studies; the NINDS 2005 special program review on ICH agreed.(Morganstern 2005)

C.1.2.1. Clinical experience with thrombolytic therapy for subarachnoid hemorrhage. Several reports of intracisternal thrombolysis in the setting of SAH were prompted by the hypothesis that hastening removal of blood clot from intracisternal compartments will reduce the incidence of cerebral vasospasm.[12-21] The most recent randomized trial comparing a single intra-operative dose of rt-PA against a placebo injection showed a trend toward a reduction in angiographic vasospasm, and a consistent trend favoring rt-PA was noted for multiple prespecified secondary endpoints. Safety was demonstrated by no significant difference in the bleeding complications between treatment and placebo group.[12]

C.1.2.2. Clinical experience with anti-thrombolytic therapy for subarachnoid hemorrhage. The potential utility of thrombolytics in reducing the degree of communicating hydrocephalus is also supported by a study of intrathecal *anti-thrombolytic* therapy to stabilize the clot after aneurysmal SAH.[22] An unanticipated finding was that *anti-thrombolytic* therapy significantly increased the incidence of delayed communicating hydrocephalus in

Appendix 1; Rationale for 1.0 mg Dose Selection

comparison to the control group; this suggested the reasonable hypothesis that *pro-thrombolytic* therapy could reduce the degree of communicating hydrocephalus.

C.1.2.3. Clot formation and clot dissolution. Our target is the brain's ventricular space. Much of what we know is derived from biochemical measurements of similar intravascular events. The normal vascular endothelium maintains blood fluidity by inhibiting blood coagulation and platelet aggregation and promoting fibrinolysis. The hemostatic system comprises a highly regulated series of procoagulant and anticoagulant zymogens and cofactors. Hemostasis (physiologic response to vascular injury) and thrombosis (pathological formation of thrombus) result from activation of this system. The balance between the coagulation cascade and the fibrinolytic pathway determines the rate of formation and dissolution of the thrombus. Blood coagulation and fibrinolysis are initiated and modulated by compounds embedded in the external membrane of cells (tissue factor, thrombomodulin), deposited in extra cellular matrix (heparin sulfate, dermatan sulfate, protease), or secreted by vascular cells in a regulated manner (von Willebrand factor, plasminogen activators, and plasminogen activator inhibitors).[23] Preliminary data establish that exogenous administration of low dose rt-PA increases CSF rt-PA from inactive range to active fibrinolytic levels (i.e., > 6 µg/mL).[24] We have demonstrated concurrent increases in clot lysis products and reduction of clot size with computed tomography in treated patients.

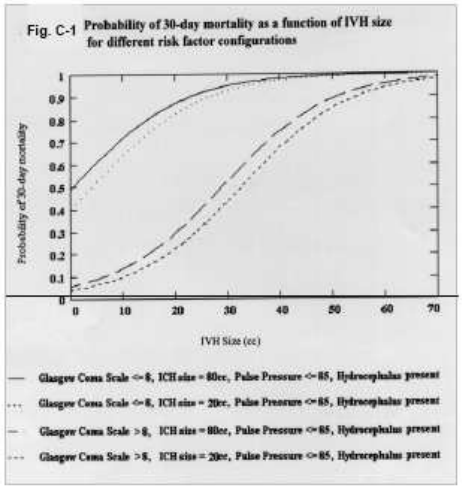

Figure C-1. Direct effect of increasing volume of IVH size on 30-day mortality. The lines represent specific groupings of disease severity factors. Despite the independent effect of GCS or initial ICH size, the contribution of IVH volume to mortality is significant and accounts for 50% or more of the mortality

C.3.1. Significance of IVH: Tuhrim hypothesis--IVH volume and mortality. The stroke data bank assessment of ICH natural history, sponsored by the NIH in the 1980's and carried out by Tuhrim, characterized stroke severity factors in hemorrhagic stroke.[25, 26] These and other studies identify IVH an independent determinant of mortality (outcome) in ICH patients.[27-30] An effect of IVH size on mortality exists independent of ICH hematoma size.[30] The importance of this factor is confirmed by the continuous relationship between IVH volume and the effect it produces, i.e., mortality.[29] A direct relationship for IVH sizes from zero to 50 or 60 cc is shown in our study (Fig. C-1).[30] The increased volume of an IVH within this range accounts for a 50 to 100% increase in mortality, supporting the idea that decreasing the volume of IVH blood could decrease mortality.

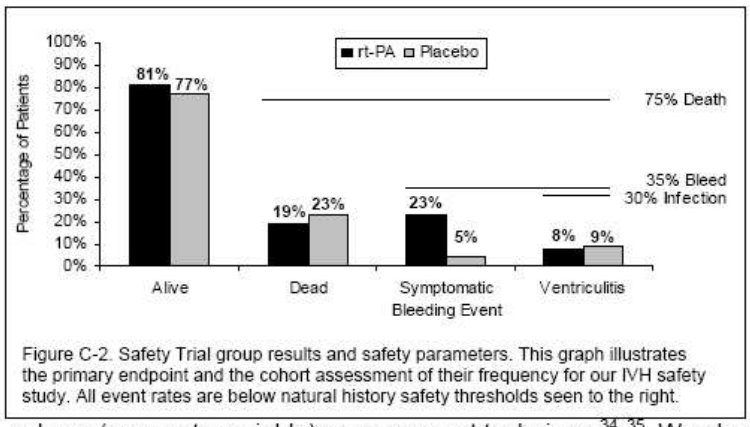

Figure C-2. Safety Trial group results and safety parameters. This graph illustrates the primary endpoint and the cohort assessment of their frequency for our IVH safety study. All event rates are below natural history safety thresholds seen to the right.

C.3.2. UK trial: first multicenter clot lysis. We organized a small proof-of-concept study in 1994 to test reversibility of the Tuhrim ICH severity hypothesis: that IVH is an ameliorable disease factor.[25, 26, 28, 31, 32] Our study demonstrated an estimate of mortality reduction compared to historically expected disease-severity-adjusted mortality,[33, 34], confirmed a possible relation of enhanced clot lysis to mortality outcome, and validated our clot volume (surrogate variable) measurement technique.[34, 35] We also found that drug administration was related to accelerated clot lysis. This study ended prematurely because UK was withdrawn from the market following FDA manufacturing concerns. ICP appeared to be well controlled throughout the protocol. Closure of the IVC drain was tolerated without incident. ICP elevations were infrequent and not different between treatment and Placebo groups. (See Appendix C.2: Ziai et al.)

C.3.3. Safety Trial: Prospective safety demonstration rt-PA. Haines and Lapointe from our investigative group reviewed the safety and efficacy of thrombolysis in the Cochrane collaboration format, which defined the need

Appendix 1: Rationale for 1.0 mg Dose Selection

for prospective studies.[36] Therefore, we prospectively studied the benefits of IVH clot removal in 48 patients who had EVD placed as routine care. Our Safety trial was a blinded multicenter, monitored, and adjudicated trial. The trial compared best medical/ICU care with aggressive ventricular drainage to best medical/ICU care with aggressive ventricular drainage plus rt-PA 3 mg Q12° via intraventricular catheter (Appendix E.3, Safety Trial Analyses & Results).

C.3.3.1. Primary endpoint: Safety hypothesis. Mortality, bleeding events during the treatment period, and ventriculitis were the pre-specified safety outcomes. Frequency of death and ventriculitis were substantially lower than expected and bleeding events stayed below the pre-specified threshold (Fig. C-2). Severity factors were evenly distributed between treatment groups at presentation and predicted 30-day mortality was 70% in both treatment arms.[28] Mortality was 19% in the rt-PA arm and 23% in the placebo arm; ventriculitis occurred in 8% and 9% and symptomatic bleeding was reported at 23% and 5%. The symptomatic bleeding event rate approached statistical significance (p=0.1). Asymptomatic bleeding showed a similar trend with five rt-PA events and two placebo events. Nervous, cardiovascular, and respiratory system adverse events and general medical events were frequent in both arms (69%, rt-PA; 91%, placebo). None of these differences reached statistical significance.

C.3.3.2. Clot size reduction hypothesis. The rate of clot resolution estimated for the first four days was significantly increased (8%/day, placebo; 18%/day rt-PA; p< 0.001). The more efficient removal of blood was associated with successful EVD removal at the end of test article administration (20% vs. 50%), less reliance on three or more EVDs, (32% vs. 4%), and a shorter length of treatment.

C.3.3.3. Model of relation between clot resolution and consciousness. Because IVH clot removal has a robust effect on consciousness in the animal model, we tested this effect on our subjects. The Glasgow Coma Scale, (GCS), closest to start of rt-PA treatment (in 44 0f 47 subjects this was within 2-h of treatment initiation) was our reference assessment of consciousness. By four days of treatment the GCS improved 1.1 points (95%, CI 0.49-1.63) for each 10%/day increase in the rate of clot resolution (p<0.001). Starting GCS was a second significant factor in the model. Baseline ICH volume was not found to be an independent factor associated with change in GCS over the period examined, once the baseline GCS was taken into account. The composite testing of all terms in the model with a Wald test had a Chi^2 (5 df) = 50.68 (p-value < 0.001). The safety data represent the first prospective, externally validated, evaluation of this approach and provide additional data on the amount and timing of blood clot removal produced by rt-PA or EVD alone. The improved mortality compared to historical controls and the partial return of the subject's consciousness, during the treatment time frame, appear to be benefits of very rapid removal of blood. These findings provide a strong rationale for a Phase III trial employing low-dose rt-PA.

Table C-1. Dose Selection Results from Safety and Clear Trials.

Group	Placebo (n=22)	3.0 mg (n= 26)	1.0 mg (n=8)	0.3 mg (n=8)	1.0mg q 8-h (n= 12)
Daily total clot lysis rate for first 3 days (%/day)	8%	23.0%	22.6%	27.5%	19.6%
Daily total clot lysis rate for first 3 days adjusted for absolute volume, assumes 50 cc clot * (%/day)	7.3%	19.2%	18.6%	15.9%	21.7%
Bleeding, symptomatic (% events)	1 (5%)	6 (23%)	0	0	1(8.3%)
Death at 30 days	5 (23%)	5 (19.2%)	1 (12.5%)	1 (12.5%)	3(25%)
rt-PA at 80 min post dose (µg/mL)	0	54	48	40	N/A
rt-PA at 3 h post dose (µg/mL)	0	21	5	0.8	N/A
rt-PA at 8 h post dose (µg/mL)	0	1	0.7	0.3	N/A
Time to 3rd/4th ventricle clearance (days post Dx CT)	6	1.3	2.2	3.4	2.2
Regional Clot Lysis Rate (Regions near the Catheter i.e., 3rd and 4th ventricle) for first 2.5 days (%/day)	N/A	N/A	32.2 %	26.5%	49%
Bleeding Safety Protocol	Basic Stability ICH stability only	Basic Stability ICH stability only	Enhanced Stability ICH, IVH and Cath	Enhanced Stability ICH, IVH and Cath	Enhanced Stability ICH, IVH and Cath
Mean IVH size [95% CI] Median	50.3 [34.9-65.8] 37.6	57.1 [42.0-72.3] 52.6	34.0 [18.6-49.5] 32.6	33.6 [6.7-60.4] 28.4	58.6 [34.2-83.0] 52.7

C.3.3.4. Safety of ICP management. ICP-rt-PA study. Forty-eight patients were enrolled in this study. A mean of 12 injections per patient were made, each with subsequent catheter closure. On 15 of 575 occasions the catheter was opened before 1-h of closure to control ICP, thus elevated ICP on IVC closure was rare. Compromise of cerebral perfusion pressure (CPP) was even less frequent during IVC closure. The percentage of closure-related elevations greater than 30 mmHg was 46/575 (8%) overall, with 28/272 (10.3%) in the rt-PA group and 18/303 (5.9%) in the placebo group. Decreases of CPP lower than 60 mmHg showed a similar

Appendix 1: Rationale for 1.0 mg Dose Selection

pattern: 18/575 (3%) overall; 5/272 (1.8%) in the rt-PA group; and 13/303 (4.3%) in the placebo group. Four patients (3 rt-PA, 1 placebo) underwent craniotomy for uncontrolled intracranial hypertension not responding to drainage and medical management; in each case an episode of symptomatic intracranial bleeding had occurred as determined by central analysis of serial CT scans. In 3 of 4 instances, surgery was successful in providing long-term control of intracranial pressure.

C.3.3.5.Defining a threshold for bleeding.. The significantly enhanced clot lysis was thought to be a surrogate for our clinical goal of clot removal. Because we noted an increase trend towards secondary bleeding events we had to address the balance between efficacy and safety before any definitive trial could become possible. In this 30-day safety study period, secondary bleeding events included: primary site rebleeding, secondary site bleeding (predominantly catheter tract) and later-discovered primary hemorrhage extensions (two of eight instances; via central CT reading). Multiple factors were implicated as risk factors for bleeding, including blood pressure, coagulation state, gender, ethnicity, diabetes mellitus, and medications such as aspirin, BP-elevating drugs and/or illicit drugs; but a definitive relation to a specific factor was not evident, nor was data on the management of these factors and their interactions with lower dose rt-PA available. Additionally, we did not have dose-response data demonstrating any relationship between intraventricular rt-PA dose and bleeding events or clot lysis rate. Thus, it was possible that a lower dose could be associated with a high degree of clot lysis but have greater safety with respect to rebleeding. Similarly, data demonstrating the time-action properties of low dose rt-PA and/or evaluating cumulative effects of low dose rt-PA was absent at the time. Thus the FDA Orphan Drug Program funded a dose finding study to resolve these issues.

C.3.3.6. Value of daily CT reading. In the Safety trial, we noted additional asymptomatic bleeding well after the initial ICH, a pattern expected with the use of a thrombolytic drug but also as part of ICH natural history. The Safety trial is the only trial to have used daily CT monitoring for asymptomatic bleeding. CT readings for 48 patients showed a 14.6% *symptomatic* bleeding rate with an additional 15% *asymptomatic* bleeding rate. Both rates are below the expected early bleeding rates in untreated patients.[37, 38] These bleeding rates may not be high compared to other convenience samples where daily CT imaging, external site monitoring, and central blinded reading were not done. The numerically increased rate of bleeding in the Safety Study prompted protocol changes: in the CLEAR IVH A trial, we intensified explicit screening to identify clot expansion at the ICH site and added the same screening before the first and each subsequent dose. We also added the requirements for daily measurements of the IVH clot width and inspection of the catheter tract region of the CT scan. Sequential local CT evaluations determined when clot lysis was complete and/or the presence of new asymptomatic bleeding. These new safety measures satisfied two data collection goals: 1) comparing daily drug administration with safety measurements and CT blood clot data points, and 2) collecting the primary surrogate outcome measure on a fixed daily schedule, optimizing CT measurements. This additional training to better utilize daily CTs for safety and drug administration decision making was organized to improve safety performance with regard to stability determination and to identify early signs of catheter track bleeding (Appendix F, CT Training Description and Reading Center Manual of Procedures). Thus, CT scans became the gauge to limit drug exposure when clot lysis goal(s) were reached.

Appendix 1: Rationale for 1.0 mg Dose Selection

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REPORT OF CLEAR IVH SURGICAL REVIEW COMMITTEE

A committee of neurosurgeons and others with critical patient care experience using EVD's was convened to address issues developed by the CLEAR IVH endpoint committee and the CLEAR IVH steering committee. Completion of CLEAR B cohort #1 and review of all prior study patients led to steering committee discussions regarding the emergency insertion of EVD's, the replacement of EVD's and the use of dual catheters. After considering these issues, the steering committee decided that the complexity of EVD catheter use would benefit from a thorough examination by experts. Because the CLEAR study is designed to use "best practices" in a uniform manner, the steering committee requested a review of EVD utilization by experts in neurosurgery and critical care with respect to clinical care in this study.

The surgical committee reviewed the data from 74 patients admitted to the Safety and Efficacy study and the CLEAR A & B studies as of 9/1/2006. This data included: a) Evaluation of catheter placement location data as well as ICP and CPP control data. b) Global intraventricular clot clearance data and regional intraventricular clot clearance data. c) Cases with dual catheters and cases with apparently slow clot lysis. Critical data from this review is summarized in Appendix I. **No changes in the investigative protocol for the current study phase (Clear B cohort #2) were deemed needed.**

The surgical committee emphasized that the operator for EVD placement be the senior skilled surgeon immediately available to perform the EVD procedure. The committee reconfirmed that when more than two passes were required such a patient was not a candidate for this study. The surgical committee noted that routine use of uniform, standard of care practices is integral to the patient care in this study. After review of the clinical data from the first 74 patients, the surgical committee noted the data confirms several commonly held opinions of "best practice." Therefore, the committee offers guidance to all neurosurgeons and investigators caring for CLEAR patients in three areas of surgical practice regarding EVD placement: 1) emergent EVD placement, 2) subsequent catheter placement, and 3) use of dual catheters.

1. Emergent EVD placement.

Emergency placement of EVD catheters should continue as in the initial 74 patients; this means placement using a twist drill procedure with target guidance predicated on surface landmarks and catheter distance markings to direct the placement. The principle of emergent placement of the EVD catheter to control ICP and allow clinical treatment of IVH was affirmed. The committee notes that ICP control was achieved with

Appendix 1: Rationale for 1.0 mg Dose Selection

this procedure with a high degree of frequency. Diligence in monitoring is still required, as all ICP elevations were not eliminated in our patients. Retrospective modeling does demonstrate that extensive removal of clot is associated with a trend towards higher likelihood of good outcomes. The committee also notes that the anatomic target for catheter placement, the foramen of Monroe, is achieved only infrequently. Finally, because of the high frequency of small amounts of asymptomatic catheter region bleeding, the committee notes that some situations will allow for the placement of the EVD in the OR via burr hole. The committee expects that, the clinical situation and OR availability will not frequently permit the use of this second option.

2. Subsequent catheter placement.

Catheter replacement can occur in one of two scenarios: emergent or non-emergent. All *emergent replacements* should continue to be defined by the surgeon's clinical judgment. The surgeon of record will determine if an emergency exists. Where replacement is needed emergently, the next step is to determine the route and procedure needed to replace the catheter. **It is expected that the majority of replacements will occur using the twist drill procedure as defined for the initial placement.** The second scenario considered was *non-emergent, surgically indicated replacement* of a catheter. (Indications include: obstruction, malposition, infection, unplanned removal or migration from an acceptable to an unacceptable position). **In this scenario the committee recognized that options utilizing image guidance and instrumentation to perform burr holes in the OR be considered in this subset of patients.** For the non emergent scenario the committee continues to suggest that a minimum period of 3 hours after prior dosing be observed to minimize interaction between bleeding risk and dosing. For all replacement scenarios and replacement surgical sites selected, the use of a large bore catheter should be strongly considered when obstruction with a clot is the reason for replacement.

3. Use of dual catheters.

Dual Catheters were a potential treatment option from the initiation of this study. The surgical committee reaffirmed that dual catheters are allowed in this study when indicated by the clinical judgment of the treating surgeon. Rules for administration of the dose of t-PA remain unchanged by the number of catheters: the doses should be alternated between catheters until blood removal goals are achieved, then single catheter dosing can be resumed. Doses should not be divided and given in both catheters simultaneously. Doses should not be "doubled up" and given simultaneously. Study design requires uniform daily dosing not to exceed 1 mg every eight hours in the current cohort. Indications for dual catheter use include: larger clots producing trapped ventricles,

Appendix 1: Rationale for 1.0 mg Dose Selection

clinically important shift, or pan-ventricular enlargement with cortical effacement/ischemia. These indications appear to occur more frequently in patients with IVH sizes larger than 40 ml, thus this clot size could be used as a trigger to consider the need for dual catheters. When the need for dual catheters is identified, which is usually after initial stabilization, **the committee recognized that surgical placement options, utilizing image guidance and OR instrumentation, be strongly considered assuming the candidate patient has stable ICP.**

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SAFETY TRIAL ANALYSES & RESULTS

All statistical results prepared by
Penelope Keyl, PhD,
President, Keyl Associates

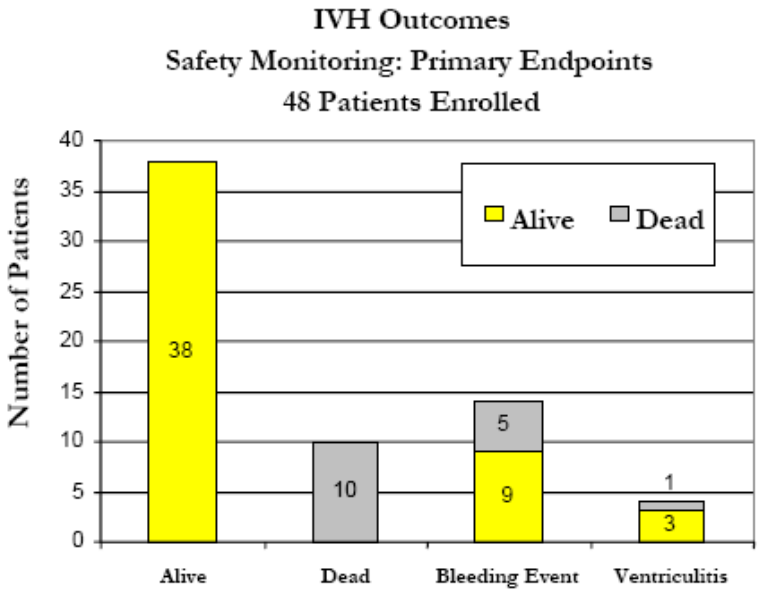

Fig. 1. Outcomes for all 48 patients enrolled. All primary endpoints were below the pre-specified level for study stop and safety review: death 21% actual vs. 75%, bleeding event 29% actual vs. 35%, and ventriculitis 8% vs. 30%.

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Appendix 1: Rationale for 1.0 mg Dose Selection

SECTION 1: OVERVIEW

The data assembled represents fully adjudicated endpoint data for the prespecified safety endpoints. Multiple blinded central evaluations of the radiologic data are currently ongoing.

The recently completed Phase IIa safety and efficacy study achieved the intended goal of demonstrating multicenter proof of effective clot removal and a safety profile of equal or greater benefits in the rt-PA treated group. Until this trial, no controlled, blinded multicenter clinical study of brain hemorrhage had measured and manipulated brain blood clot volumes in a systematic manner that associates volume reduction with assessments of beneficial outcome. Additionally, data on the safety, pharmacokinetics, and clinical response to intracranial administration of rt-PA did not exist. The data presented here reverse this absence of information and add important information to the knowledge base of clinicians and researchers who are treating intracerebral hemorrhage. Our major findings are as follows:

1. Recombinant tissue plasminogen activator (rt-PA) increases the rate of blood clot removal from the ventricle at a rate of 10% to 18% per day.
2. Recombinant tissue plasminogen activator (rt-PA) can be administered in doses of three milligrams every 12 hours without adversely affecting the mortality of intracerebral hemorrhage (ICH) with intraventricular hemorrhage (IVH). Multiple clinical benefits are possibly associated with drug administration.
3. Evidence of the major side effect of rt-PA in other disease processes is also found in the investigation of ICH with IVH: increased drug associated bleeding events.

Ongoing studies will be improved by applying this data to study design. It is likely that changes in drug administration will increase efficacy and decrease side effects, specifically: lowering doses of rt-PA and shortening the time interval between administrations.

Hypothesis 1: rt-PA for IVH is safe.

Part 1. Primary safety endpoints by treatment group.

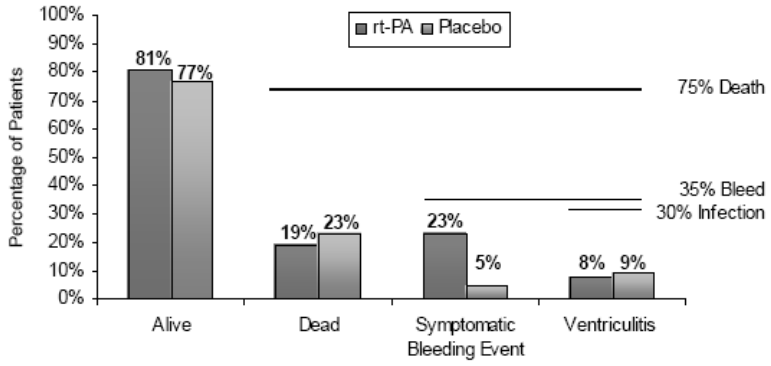


Fig. 2. Outcomes for all 48 patients enrolled. All primary endpoints were below the pre-specified level for study stop and safety review: death 75%, symptomatic bleeding event 35%, ventriculitis 30%.

Appendix 1: Rationale for 1.0 mg Dose Selection

Hypothesis 2: rt-PA increases the rate of blood clot resolution for IVH.

Part 2. Relation of current clot resolution to clinical goal of 80% resolution in 72 hrs.

As shown in figure 3, patients receiving rt-PA achieved clot resolution of 40% at 3 days versus the 80% predicted (as indicated by the dot-dash blank line demonstrating clinical goal).

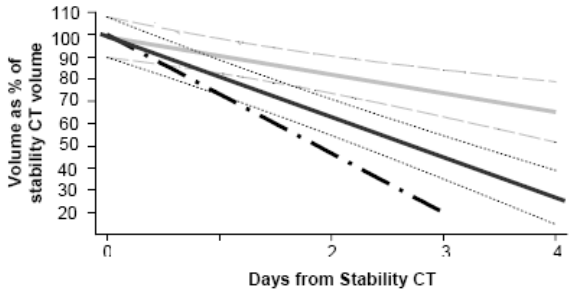


Fig. 3. Daily IVH volume as percent of stability CT for 4 days following stability CT in the active treatment (n=26) and placebo (n=22) groups. Bold dashed black line indicates Clinical Goal. Solid gray line indicates the placebo with dashed gray lines showing 95% CI. Solid black line shows the rt-PA with dotted black lines indicating 95% CI.

Appendix 1: Rationale for 1.0 mg Dose Selection

Overview of Clear IVH Part A
June 20, 2005

Patient characteristics. This study was a double blind randomized dose finding study that evaluated two additional (lower) doses of rt-PA for clot lysis rate and safety. Patients were randomized to either 0.3 mg or 1.0 mg IVC q 12hrs for up to eight doses or until the IIIrd and IVth ventricle were open. The study started on February 2004 and finished on March, 2005. A group of nine men and seven women were recruited. They had an average age of 53 years (48 for 0.3 mg and 57 for 1.0mg).

Severity factors (mean) at time of diagnosis for the total cohort of 16 subjects were GCS (9.6), IVH size (32 cc), BP (200/107), and ICH size (11cc). The groups were well balanced with respect to initial severity, initial medical stabilization and demographic characteristics. Each dose group had a trend towards smaller IVH volumes than the 3 mg cohort that preceded this study, 32 vs. 53 cc clot size. The initial location of bleeding was thalamic in a majority of subjects and there were more patients with drug use in their history 62.5% versus 27% for the 3 mg group.

Protocol performance. The CLEAR protocol required clinical placement of the EVD for treatment of acute obstructive hydrocephalus, used q 12 hour drug administration regimen with 1 hour of EVD closure after each dose. Unlike the safety study patients, CLEAR patients were entered for a longer time window post bleed: up to 48 hours. American Stroke Association ICH guidelines and AANS ICP management guidelines continued to be the basis for establishing uniform critical care management of patients. Protocol additions used for the first time in CLEAR A were 1) Explicit process for clot measures at ICH and IVH sites needed for determination of 6 hour stability. 2) The use of a stability algorithm for assessment of EVD catheter track bleeds. 3) Explicit definition of drug termination criteria: (i.e., IIIrd and IVth ventricular opening). Compliance with drug administration, CT acquisition and AANS ICP management guidelines was high.

Results. Direct comparison of the initial clot lysis rate (first three days of treatment) estimated dose specific rates of 23, 27.5 and 22 % (of stability CT scan volume)/day for the 3 mg, 1.0 mg and 0.3 mg groups. The safety profile for the two lower doses was numerically superior to the 3 mg dose. Specifically no symptomatic bleeding occurred at either dose level (0.3 mg or 1.0 mg). A blinded central analysis of C/D data did not demonstrate a significant difference in catheter tract bleeds between groups. A trend for minor bleeds (>5mm, confluent) to occur with 1.0 vs. 0.3 mg drug exposure can be observed. There were no episodes of bacterial ventriculitis for either dose. One death (13%) occurred in each group.

From a direct comparison of the efficacy and side effect profile of the three doses the 0.3mg dose appears to offer the highest rate of clot lysis with lowest complication rate. This was the pre-specified performance measure to be used in the dose selection process. However other considerations may come into play. These include: PK results, timing of IIIrd and IVth ventricle opening and cohort heterogeneities (in clot size and gender) which need to be considered with respect to their possible influence on the efficacy and safety results.

Appendix 1: Rationale for 1.0 mg Dose Selection

From an efficacy perspective gender appears to be associated with an increased baseline clot lysis rate and with a tendency to experience fewer clot enlargements/rebleeds. The 3mg group had a male 73% to female 27% ratio. Thus, comparisons between groups could have a correction for gender disproportion. A second factor possibly associated with variation of clot lysis rates is initial clot size. Inspection of the rt-PA treated clot lysis rates from each dose group suggests that smaller size clots (i.e., < 50 cc) have faster lysis rates. This observation was recently made for the first time, thus it would be best to reconfirm the reproducibility of this finding with CLEAR part B data. However, as this looks like a robust factor influencing the clot lysis rate, our most important clinical surrogate, we believe the 0.3 mg and 1.0 mg data should be corrected for the smaller clot sizes found in these cohorts. See figure 1 and table 1.

From a safety perspective, the CLEAR cohorts have more women than men. Thus there is a possibility that the apparent improved safety profile is related to gender (greater number of women) or to the combination of small sample size and low intrinsic safety "event rates." Additionally new safety measures were instituted to better determine initial cessation of bleeding and to identify catheter tract enlargement early in its existence. Finally drug exposure was limited by total dose (only four days dosing allowed) and by explicit study termination criteria, that when applied, led to earlier termination of study drug (i.e., decreased total drug doses) in this particular study. Longer periods of stabilization after EVD placement and if catheter tract bleeding was noted may have influenced the likelihood of primary site rebleeding and catheter related bleeding. None of these factors are directly related to injected drug dose, but could partially or wholly account for the improved safety profile. These factors were taken into consideration in the selection of the study dose for CLEAR part B.

Ventricular clearance data. Because the drug administration protocol called for terminating drug delivery with opening of the IIIrd and IVth ventricles, an analysis of the time to opening of these ventricles should be informative with respect to dose selection. Such timing may not have as many biases related to catheter-clot anatomic relationships. This is important to note because the CLEAR protocol required placement near the third and fourth ventricles and required discontinuation of drug after clearance of these two sites. Thus the failure to lyse residual blood in the lateral ventricles is not taken into consideration with an evaluation focused solely on the IIIrd and IVth ventricles. A blinded analysis of time to open these ventricles suggests the 1.0 and 3.0 mg doses trend toward more rapid and more complete opening. See figure 2.

Pharmacokinetics data. The optimal local dose of rt-PA for effective intervascular clot lysis is thought to be 6,000 ng/ml. Thus the PK results would be important to the decision of which dose to select. Evaluation of the 0.3, 1.0 and 3.0 mg doses suggests the 1.0 mg dose is best from the perspective of the optimal drug level of 6,000ng/ml. The 3.0 mg dose frequently exceeds this level by 100 to 1,000% and the 0.3 mg dose does not always produce a sustained elevation to this level. See PK power point attachment.

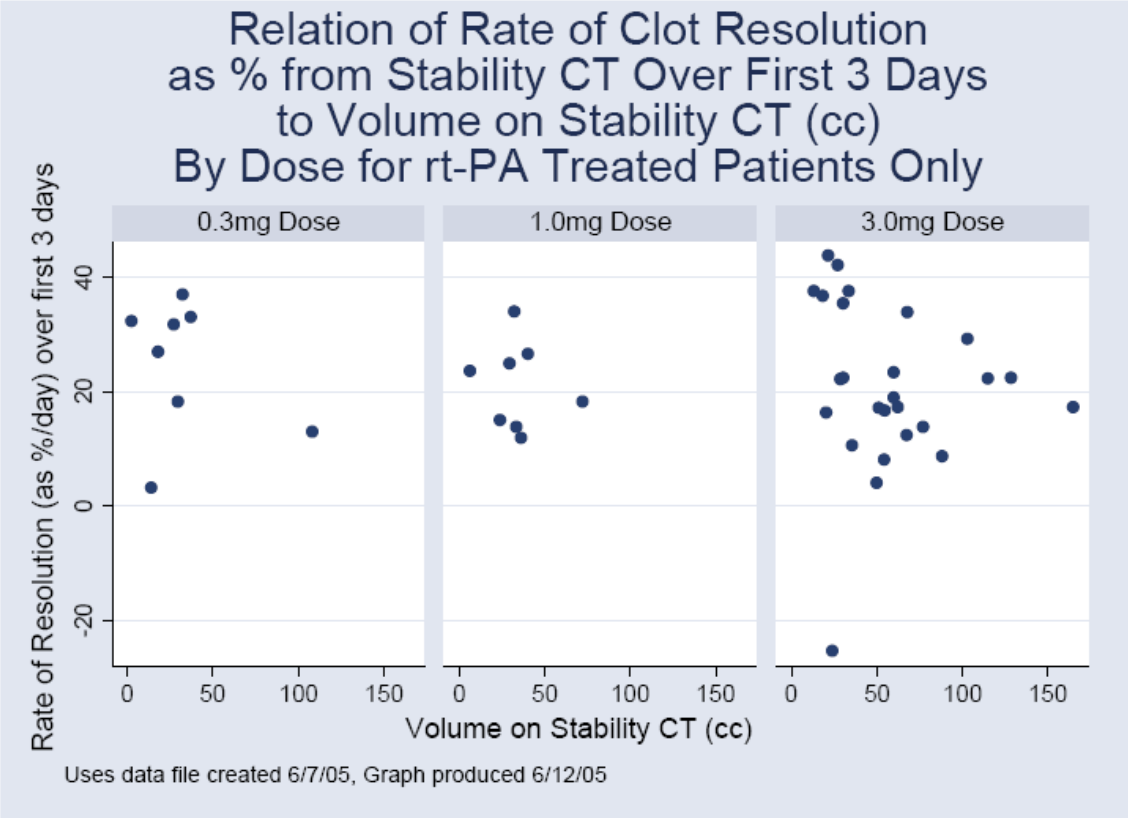
Analysis changes for future stages/phases of the CLEAR study. We propose to add a secondary analysis of clot lysis rate based on absolute volume of clot at the time of stability scan. This will continue the assessment of the form of the relationship between volume of clot lysed and clot size (see Table 1). We will add an assessment of the location of the residual clot based on centrally-determined Graeb scores to the secondary analysis of the study's primary endpoint, rate of clot resolution.

Appendix 1: Rationale for 1.0 mg Dose Selection

Plans for Part B. Dose selection. Based on this analysis we believe the 1.0 mg dose offers the best demonstrated clot lysis rate with an acceptable safety event rate. We propose to initiate the dose escalation CLEAR part B with 1.0 mg of rt-PA administered every 8 hours for tier one. We anticipate this will be followed by tiers investigating every six and four hours as previously described.

Protocol changes. The executive committee recognizes that the best clinical endpoint for discontinuation of therapy is not yet defined. We intend to continue the arbitrary clinical endpoints of clearance of 3rd and 4th ventricle and/or 80% blood clearance as the treatment endpoints to assure the uniformity of clinical approach in this study at this time. No additional protocol changes are planned. We will continue to emphasize stringent on site evaluation of CT and CT scan interval changes for stability blood clot size for both the ICH and the IVH compartments.

Figure 1. Scatter Plot of clot lysis rate versus initial volume.



Appendix 1: Rationale for 1.0 mg Dose Selection

Table 1. Model taking consideration of effect of initial volume on clot lysis rates.

Estimate of resolution of IVH, expressed as volume resolved (cc) and % of initial volume resolved three days after stability scan for 0.3, 1.0 and 3.0 mg dose of rt-PA using two alternative analytic models, and with estimates based on stability clots volumes of 25cc, 50cc, and 75cc.

Note: The clot resolution models are based on data from the first 3 days following the Stability CT scan only.

IVH Volume on Stability CT scan	Dose	Analytic Model A		Analytic Model B	
		Dependent variable: Volume at time t as % of Volume on Stability CT Scan		Dependent variable: Change in Absolute Volume (cc) from Volume on Stability CT Scan at time t	
		Estimate of total resolution over the three days after stability scan		Estimate of total resolution over the three days after stability scan	
		Estimate expressed as Absolute Volume Resolved	Estimate expressed as % of Volume on Stability Scan Resolved (%)	Estimate expressed as Absolute Volume Resolved (cc)	Estimate expressed as % of Volume on Stability Scan Resolved (%) +
25cc	0.3mg	19.5cc	77.7%	12.8cc	51.2%
25cc	1.0mg	15.7cc	63.0%	14.8cc	59.2%
25cc	3.0mg	16.1cc	64.2%	15.2cc	69.8%
50cc	0.3mg	38.9cc	77.7%	24.7cc	49.4%
50cc	1.0mg	31.5cc	63.0%	28.7cc	57.4%
50cc	3.0mg	32.2cc	64.2%	29.7cc	59.4%
75cc	0.3mg	58.4cc	77.7%	36.7cc	48.9%
75cc	1.0mg	47.2cc	63.0%	42.7cc	56.9%
75cc	3.0mg	48.2cc	64.2%	44.1cc	58.8%

A: Percent volume remaining at time t (days after stability scan)
= 104.8 – 27.5 * t, if dose = 0.3mg (0.3mg vs 3.0mg dose p = 0.25)
= 104.8 – 22.6 * t, if dose = 1.0mg (1.0mg vs 3.0mg dose p = 0.90)
= 104.8 – 23.0 * t, if dose = 3.0mg

B: Volume resolved (cc) by time t (days after stability scan)
= 0.78 + .159 * Stab. vol. * t, if dose = 0.3mg (0.3mg vs 3.0mg dose p = 0.41)
= 0.78 + .186 * Stab. vol. * t, if dose = 1.0mg (1.0mg vs 3.0mg dose p = 0.90)
= 0.78 + .192 * Stab. vol. * t, if dose = 3.0mg

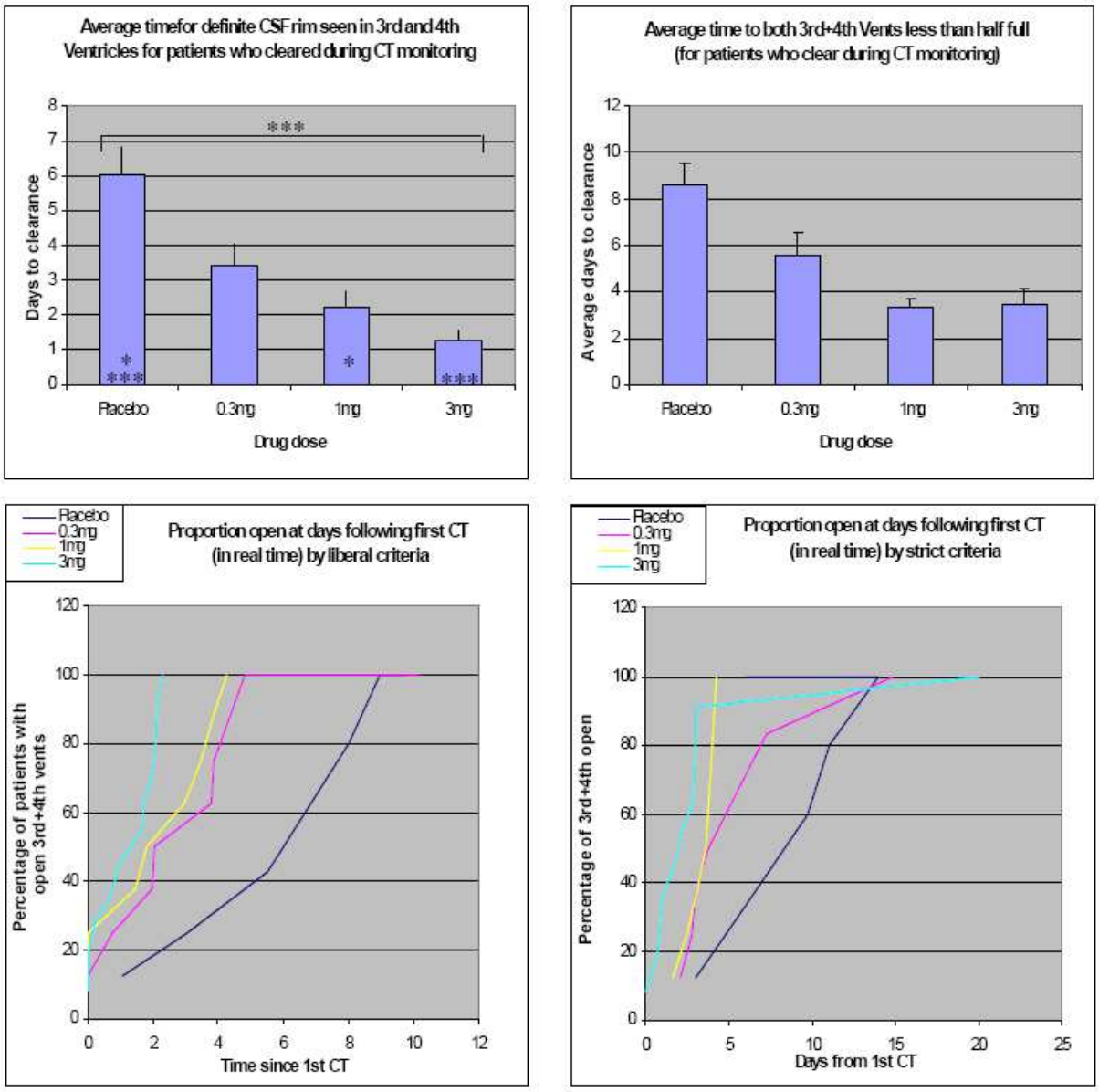
The percent of variance explained was 39% if the stability volume was not taken into account for analyses with the dependent variable= Change in Absolute Volume (cc) from Volume on Stability, versus 59% when the stability volume was taken into account.

+ Model B fits the observation that % resolution is faster for smaller clots

Analyses done 6/7/2005, Table prepared 6/13/2005

Appendix 1: Rationale for 1.0 mg Dose Selection

Figure 2. Ventricular opening



Time to opening of ventricles by Graeb Criteria, either by time until both ventricles are less than half full, or by time until a definite rim of CSF can be seen (=3/4 full or less).

***** p=0.001; *p=0.016**

Appendix 1: Rationale for 1.0 mg Dose Selection

Stage 2: Dose Tier 1 Results

July 28, 2006
(Reviewed by DSMB and Steering Committee)

Patient characteristics. Stage 2 of the CLEAR IVH protocol (CLEAR IVH B), dosing tier 1 was an open label dose interval finding study that evaluated 1 mg of rt-PA given q8h for up to eight doses or until the IIIrd and IVth ventricle were open. This stage of the protocol opened enrollment in August 2005 and completed enrollment in April, 2006. A group of ten men and two women were enrolled. They had an average age of 56.5 years.

Average disease severity factors (mean) at time of diagnosis for the total cohort of 12 subjects were GCS (9.2), IVH size (56.7 cc), BP (204/123), and ICH size (11.1 cc). This cohort was generally well balanced with respect to initial severity, initial medical stabilization and demographic characteristics when compared to the 0.3, 1.0, and 3.0 mg dose groups from our previous investigations. However, the DSMB noted an important qualitative trend towards higher severity in the CLEAR B, tier 1 group predominantly on the basis of IVH clot size. Specifically, this dose group had a trend towards larger IVH volumes than the previous cohorts that preceded this study, 56.7 cc (1.0 mg q8h) vs. 34.4 cc (0.3 mg q12h), 33.3 cc (1.0 mg q12h), and 49.7 cc (3.0 mg q12h).

Protocol performance. The CLEAR protocol required clinical placement of the EVD for treatment of acute obstructive hydrocephalus, used q 8 hr drug administration regimen with 1 hr of EVD closure after each dose. Compliance with drug administration, CT acquisition and AANS ICP management guidelines was high.

Results. *Clot lysis.* The subjects enrolled in stage 2 of the CLEAR IVH protocol (CLEAR IVH B) continue to provide evidence that rt-PA increases IVH clot resolution from about 8% per day to about 20% per day. Initial resolution remains linear over the first 4 days. Subsequently, the resolution rate slows. Dosing was most often discontinued by four days, which may account for the slowing of the resolution rate. Higher rates of clot resolution (i.e., rates of $\geq$ 30% of stability volume per day) were seen only for clots that were 50cc or less at the time of the stability scan. The mean IVH clot size for the 12 subjects enrolled in stage 2 of the protocol was 56.7 cc, which may explain why the daily rate of clot resolution was unchanged (but, arithmetically slower) when compared to the group in stage 1 (CLEAR IVH A), who received 1.0 mg of rt-PA q12hr and had a mean IVH clot size of 33.3 cc (Fig. 1).

Safety. Frequency of events in all three of the pre-specified categories, 30-day mortality, symptomatic bleeding, and bacterial ventriculitis were below the pre-specified safety levels set by the study group and the independent DSMB. The DSMB has given permission to proceed with a second tier of 12 patients.

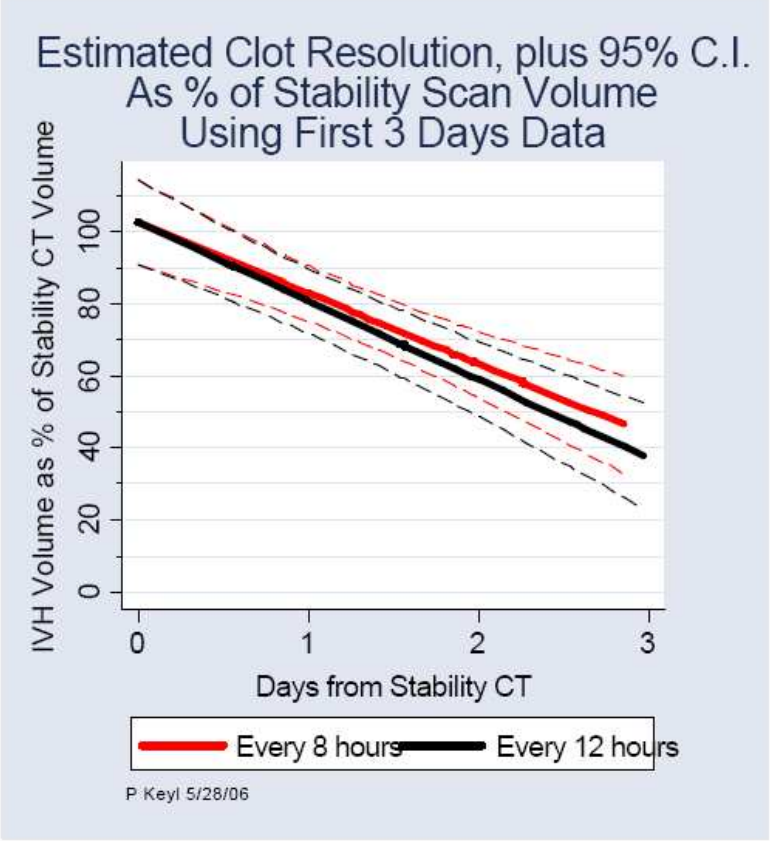
For the first tier of stage 2 of the protocol (CLEAR IVH B) events of note are one subject who experienced a symptomatic bleeding event and one subject who was diagnosed with bacterial ventriculitis. Three subjects died prior to the 30-day follow-up visit, all as a result of the severity of the initial bleeding event and withdrawal of care. Importantly deaths were not attributed to bleeding or ventriculitis. We note that the safety rates for this group of 12 subjects were higher in this cohort when compared to the 16 subjects enrolled in stage 1 of the protocol (CLEAR IVH A). It is important to emphasize that these event rates remain exceedingly low compared to historical rates. To assure that safety is optimally pursued as new centers are added, the steering committee has formulated plans to address infection and bleeding to include re-education of all investigators regarding: 1. aseptic technique, 2. monitoring of daily cerebrospinal fluid sample analysis results, and 3. detailed review of stability CT scan prior to first dose and review of daily CT scans prior to next scheduled dose to monitor for catheter tract bleeding, change in ICH size, change in ventricle size, and for resolution of the clot as an indicator to stop drug administrations.

Plans for re-opening enrollment. Based on the current analyses we believe more data are needed to further evaluate the 1.0 mg q8hr dose. We propose to expand the current tier from 12 to 24 subjects to allow for the enrollment of subjects with smaller IVH clot sizes, which will enhance comparisons with previous cohorts. The additional data could provide justification for testing different doses in the final tier or may lead only to further enlargement of the current tier.

Appendix 1: Rationale for 1.0 mg Dose Selection

Protocol changes. No protocol changes are planned. We will continue to emphasize stringent on site evaluation of CT and CT scan interval changes for stability of blood clot size for both the ICH and the IVH compartments.

Fig. 1. Estimated Percent of Stability Clot Volume Remaining by Time From Stability CT for 1.0mg Dose, by Dose Frequency

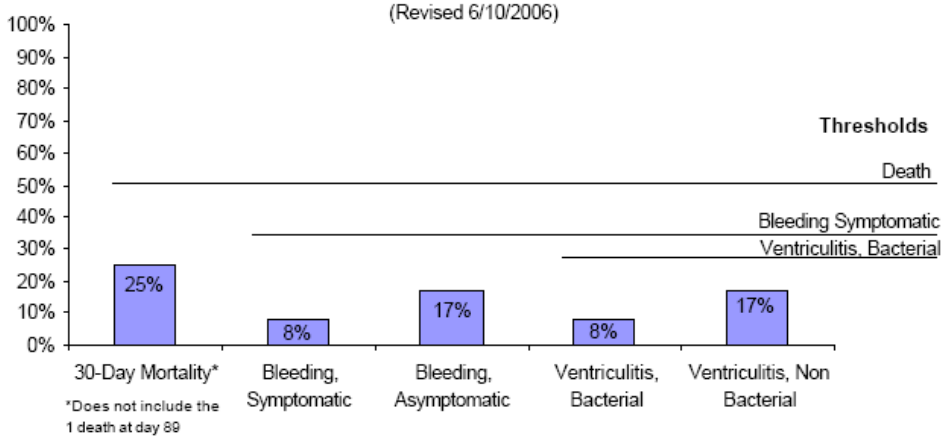


Appendix 1: Rationale for 1.0 mg Dose Selection

Summary of Safety Results

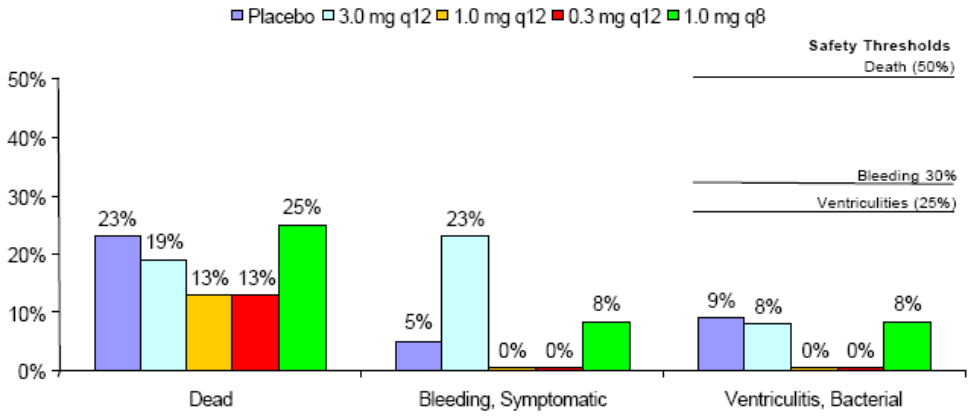
All graphs and reports are an excerpt from the report reviewed by the Data and Safety Monitoring Board for CLEAR B, dosing tier 1. The original graph numbering is preserved here for consistency.

Graph 2: Endpoint Frequency with Thresholds
CLEAR IVH B: 1 mg rt-PA q8hr
Percentage of Subjects Experiencing 1 or More Primary Endpoints
(Revised 6/10/2006)



These data for 1mg q8h (n=12) are represented below in green and compared to the previous cohorts of placebo (n=22), 3.0mg q12h (n=26), 1.0mg q12h (n=8), and 0.3mg q12h (n=8).

Primary Endpoint Comparison
Safety, CLEAR IVH A, and CLEAR IVH B Tier 1



Appendix 1: Rationale for 1.0 mg Dose Selection

Number of Adverse Events by Body System

Body System	Total # of Events	% of Events	Ave # per pt
Nervous System	14	17.50	1.6
Nervous System Hemorrhage	6	7.50	2
General Body/Miscellaneous	10	12.50	1.25
Skin/Special Senses	1	1.25	1
Digestive	6	7.50	1.5
Cardiovascular	14	17.50	1.75
Respiratory	10	12.50	1.25
Endocrine/Metabolic	3	3.75	1.5
Hem/Lymphatic	1	1.25	1
Urogenital	6	7.50	2
Other/Unclassified	10	11.25	3
Total	**81**	**100.00**	**1.6**

Number of Patients Experiencing Adverse Events by Body System

Body System	1.0mg q8
Nervous System	8
Nervous System Hemorr	2
General Body/Miscella	8
Skin/Special Senses	1
Digestive	4
Cardiovascular	7
Respiratory	7
Endocrine/Metabolic	2
Hem/Lymphatic	1
Urogenital	4
Other/Unclassified	4
No adverse event reported	2
Total Patients	**12**

	1.0mg q8	
	N	**(%)**
No adverse event	2	(16.7)
Any adverse event	10	(83.3)
Total Patients	**12**	**(100.0)**

Deaths within 30 Days

	1.0mg q8	
PrimaryCauseOfDeath	**N**	**(%)**
Initial Bleed	0	(0.0)
Withdraw care	3	(25.0)
Other	0	(0.0)
Total patients	**12**	**(100.0)**

Appendix 1: Rationale for 1.0 mg Dose Selection

Number of Patients with Pre-specified Safety Events

Event	# of Subjects experiencing 1 or more events
30-day Death	3
> 30-day Death	2
Ventriculitis, bacterial	1
Ventriculitis, non-bacterial	2
Hemorrhage, symptomatic	1
Hemorrhage, asymptomatic	2

Observed Adverse Events by Group

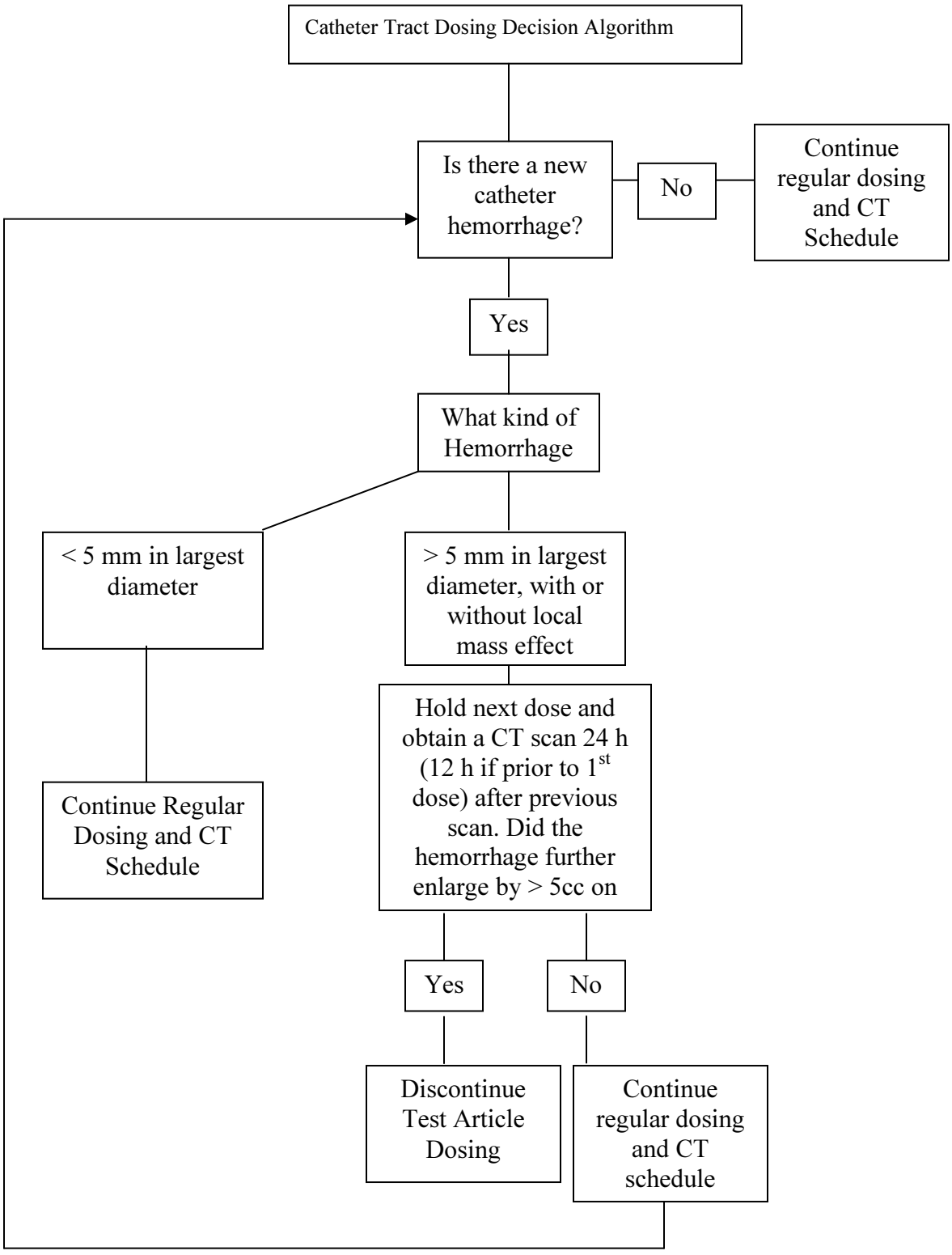
Event	1.0 mg q8hr (number serious)
Acute renal failure	1 (0)
Anemia	1 (0)
Ascites	1 (0)
Atelectasis	2 (0)
Atrial fibrillation	1 (0)
Bradycardia	1 (0)
Cardiac arrest	2 (2)
Cerebral infarction	2 (0)
Decreased level of consciousness	1 (0)
Deep vein thrombosis	2 (0)
Delirium (includes agitation)	1 (0)
Diarrhea	3 (0)
Fever of unknown origin	9 (0)
Headache	3 (0)
Hemorrhage enlargement, intraventricular - asymptomatic	2 (1)
Hemorrhage, new catheter tract < 5 mm, asymptomatic	2 (0)
Hemorrhage, new catheter tract > 5 mm with mass effect, asymptomatic	1 (0)
Hemorrhage, new intraventricular, asymptomatic	1 (1)
Hemorrhage, new intraventricular, symptomatic	1 (1)*
Herniation, brain	2 (0)
Hydrocephalus, communicating	1 (0)
Hyperglycemia	1 (0)
Hypertension	3 (0)
Hypoglycemia	1 (0)
Hypokalemia	1 (0)
Hypotension	1 (0)
Increased ALT	1 (0)
Increased AST	1 (0)
Increased BUN	1 (0)
Increased creatinine	2 (0)
Intracranial hypertension	2 (0)
Myocardial infarction	1 (0)
Pleural effusion	1 (0)
Pneumonia	7 (1)
Pulmonary embolism	1 (0)
Sinus tachycardia	1 (0)
Supraventricular tachycardia	1 (0)
Urinary tract infection	2 (0)
Ventriculitis	2 (0)
Vision abnormality	1 (0)
Vomiting	1 (0)
Other significant adverse event: 10 (2)	
Respiratory arrest due to withdrawal of care	1 (1)
Elevated troponin	1 (0)
Increased midline shift	1 (0)
Cerebral ischemia	1 (0)
Hypokalemia	1 (0)
Expansion of the EVD related hematoma	1 (0)
Blown right pupil	1 (0)
Cerebral ischemia	1 (0)
Increased midline shift	1 (0)
Suspected cardiac or pulmonary emboli	1 (1)*
Total	**81 (8)**

Appendix 1: Rationale for 1.0 mg Dose Selection

Serious Adverse Events by Subject

	Subject	Date of Report	Event	Seriousness	Expected/ Unexpected	Related to rt-PA therapy
1	173205	12/28/05	New IVH, asymptomatic (Pending reclassification as New IVH, symptomatic)	Life threatening, prolonged hospitalization, other: needed new IVC	Expected	Probably
2	157207	1/19/06	Hemorrhage enlargement, intraventricular - asymptomatic	Life threatening	Expected	Probably
3	102209	2/23/06	Cardiac arrest	Death	Expected	Not Related
4	157207	2/23/06	Hemorrhage, new intraventricular – asymptomatic (Pending reclassification as Other: Direct effect of initial bleed)	Death	Expected	Not Related
5	152211	3/16/06	Respiratory arrest due to withdrawal of care	Death	Expected	Not Related
6	173205	3/22/06	Possible cardiac or pulmonary emboli	Death	Expected	Not Related
7	100212	6/8/06	Pneumonia	Prolonged hospitalization	Unexpected	Not Related
8	102203	7/7/06	Cardiac arrest	Death	Expected	Not Related

Appendix 2: Catheter Tract Dosing Decision Algorithm



Appendix 3. Sample Consent Form

RESEARCH Subject INFORMATION AND CONSENT FORM

Title: CLEAR III (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III)

Protocol No.: IVH06

Sponsor of Record: Daniel F. Hanley, MD
Director, Brain Injury Outcomes Division
Johns Hopkins University Department of Neurology
Baltimore, Maryland, USA

Primary Funding: National Institutes of Health/
National Institute of Neurological Disorders and Stroke

Additional Support: Genentech, Inc.

Principal Investigator:

Facility(s):

Study-Related Phone Number(s):

Date/Revision: 4 APRIL 2013

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain anything that you do not clearly understand. You may have an unsigned copy of this consent form to take home and think about or discuss with family or friends before making your decision.

A person who takes part in a research study is called a research or study subject. In this consent form, "you" always refers to the research subject. If you are a legally authorized representative (LAR), please remember that "you" means the research (study) subject.

What you should know about research studies:

- You are being asked to be in a research study.
- This consent form explains the research study.
- Please read it carefully and ask questions about anything you do not understand.

- If you do not have questions now, you may ask later.
- If this study relates to a health problem you have, we will explain what other treatment could be given outside the research. You should understand those options before you sign this form.

To be in a research study you must give your informed consent. Giving "informed consent" means:

- Reading this consent form,
- Having the study doctor or staff explain the research study to you,
- Asking questions about anything that is not clear, and
- Getting an unsigned copy of this consent form to take home. This gives you time to think about it and to talk to family or friends before you make your decision.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- No one can promise that a research study will help you.
- Taking part in research study is entirely voluntary. No one can make you take part.
- If you decide to take part, you can change your mind later and withdraw from the research study.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- Other parts of this study may involve experimental (investigational) drugs or procedures that are being tested for a certain condition or illness. An investigational drug is one that has not been approved by the U.S. Food & Drug Administration (FDA).
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed, then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the research;

- What drug or device or procedures will be used;
- Any possible benefits to you, if any;
- The possible risks to you;
- The other medical procedures, drugs or devices that could be used instead of being in this research study; and
- How problems will be treated during the study and after the study is over.

If you take part in this research study, you will be given a copy of this signed and dated consent form.

Why is this research being done?
This research is being done to determine if a study drug called recombinant tissue plasminogen activator (rt-PA), which dissolves blood clots helps improve patients with brain blood clots, by rapidly removing the clot when compared to placebo (a fluid that does not dissolve blood clots). rt-PA may lead to more rapid removal of these clots. rt-PA has been approved for certain uses in humans. However, the drug has not been approved for the use that we plan in this study, and therefore is considered investigational by the U.S. Food and Drug Administration.

People with intracerebral hemorrhage (bleeding in the brain) with intraventricular hemorrhage (bleeding in the ventricles or open spaces in the brain) who are candidates to receive an intraventricular catheter (IVC, catheter inserted into the open spaces of the brain called ventricles) may join. The usual treatment for intraventricular hemorrhage is to place an IVC. This usual treatment is called “standard medical care.”

What will happen if you join this study?
About 500 patients will be enrolled in this study over a 6-year period. With your consent, you will have the following screening procedures to find out if you are eligible for this study.

1. In order to be considered for participation in this study, your doctor must have decided it was necessary to surgically place an IVC in your head. After IVC placement, you will have a CT scan 6 or more hours later to make sure the IVC was placed correctly and to make sure there is no new bleeding in your brain. If the IVC is not in the correct place, the IVC will be pulled out a little or removed and replaced. If this happens, another CT scan will be repeated 6 or more hours later to again make sure the IVC was placed correctly and to make sure there is no new bleeding in your brain. These CT scans may already have been done per standard medical care.

2. A pregnancy test will be done if you are a female of childbearing potential. You must not be pregnant to be in this study.

3. Your initial evaluation will include a physical medical history, physical examination, blood tests to see how your blood clots, urine for drug testing, and tests of your neurological condition.

If, after these tests, you are found to be eligible for this study, you will be randomly assigned (similar to flipping a coin) to one of two groups being compared in this study. You will either receive injections of rt-PA through the IVC to help break-up the clot or injections of saline (salt water) fluid through the IVC. Normal saline is a placebo, which is a fluid that does not have any medicinal effects. We will inject about a teaspoon of rt-PA or placebo into the ventricles through the IVC every 8 hours up to 12 times. After each injection, the IVC will be closed for up to 1 hour, as tolerated, in order to allow the rt-PA or placebo to mix with the blood clot. We will stop the injections when the IVC is no longer needed or when enough blood has drained from the ventricles.

Regardless of what group you are assigned to your vital signs, such as, heart rate, blood pressure, temperature, and neurological condition will be monitored daily for the next 7 days. Laboratory blood samples will be drawn for the next 7 days to monitor natural chemical levels in the blood related to the bleeding in your brain. CT scans will be done daily for the next 5 days to monitor the remaining blood clot in your brain.

Normal care includes the use of intravenous antibiotics to reduce the risk of brain infection. A head CT scan will be done about every 24 hours to watch for any changes in the blood clot in the ventricles and for additional bleeding. A CT scan is a test that produces an image of your body using a small amount of radiation. The image shows the body tissues and structure in three dimensions ("3-D"). An additional CT scan will be done if your condition changes (either worsens or improves). This is about twice the number of CT scans a patient would normally have as standard of care for this condition.

You will be asked to return to clinic 1, 6, and 12 months from today for a follow-up visit. At the 1-month and 12-month visits only a follow-up head CT scan will be done to see if there have been any changes in your brain. At each visit we will also do neurological examinations to see how you are doing. These visits will take about 2 hours and will be video recorded. This tape will be sent to an expert doctor in the United Kingdom for review. If during the 30-, 180- and 365-day follow-up visit, we are unable to interview you directly, we will ask permission to interview the person accompanying you during the visit. There will be a separate consent form for the person accompanying you to sign at that time, if it is necessary.

You will be contacted by telephone 3 and 9 months from today. You will be asked questions about your condition and how well you are doing. These phone calls will take about 30 minutes.

What are the risks of the study?
Because rt-PA dissolves blood clots, there is a risk that it may cause new bleeding in the brain or elsewhere in the body. New or "symptomatic" bleeding in the brain causes new stroke symptoms (loss of speech, paralysis of one side of the body), coma, or death. This new bleeding occurs during the first 24 hours in about 40% of patients with untreated intracerebral hemorrhage. Published journal papers suggest brain bleeding occurs in 5% to 10% of subjects after receiving a similar dose of rt-PA injected into the brain. In two new, recent studies using rt-PA a 23% increase in new bleeding in the brain with clinical symptoms was observed (3.0

mg dose), 0% symptomatic new bleeding for the 1.0 and 0.3mg dose in 16 patients, and 8.3% symptomatic new bleeding for the 1.0mg dose in 36 patients. Thus there is a potential for new bleeding in the brain with and without treatment. Bleeding outside of the brain has been very uncommon. With standard treatment, the chance of dying or of having a significant permanent disability from blood in the ventricles ranges from 50-80%.

The injection of this drug may also increase the risk of infecting the ventricles. The risk of ventricle infection without injection of rt-PA or placebo is approximately 10% to 20%. The risk is about 8% when hydrocephalus with no intraventricular hemorrhage is the reason for catheter treatment. In our previous studies, ventriculitis occurred in 3% to 9% of patients who received rt-PA injections. The removal of CSF may be associated with an increased risk of infection in the ventricles. We will try to further reduce the risk of infection by using a standardized sterile technique to inject the drug and remove the CSF.

We will watch for problems by sampling the spinal fluid for infection, testing the blood for bleeding disorders, and by CT scans of the brain to look for additional bleeding.

The intracranial pressure (ICP), the pressure inside the head, could go up while the IVC is closed for up to 1 hour after each injection of rt-PA or placebo. We will monitor the ICP continuously while the IVC is closed. If the ICP rises to unsafe levels and does not respond to routine treatment, your doctor will re-open the IVC for your safety. Closing the IVC for 15 to 60 minutes at a time is part of the standard management of all patients with IVCs.

The radiation exposure from the x-rays you will receive by participating in this study is equivalent to an exposure of 2.16 rems to your whole body. For comparison, naturally occurring radiation from the environment exposes people to about 0.3 rems per year, and people exposed to radiation in their occupations are permitted to receive whole body exposures of 5 rems per year.

You will have to stay in bed while the IVC is in place. All other medical care will be routine for subjects with your condition in the intensive care unit.

Drawing blood from your arm may cause pain, bruising, lightheadedness, and, on rare occasions, infection.

We do not yet know if your overall risk is higher or lower if you get the investigational medication. Other risks include possibly worsening of your neurological condition and potentially even death. An IVH patient receiving standard medical care is at risk for these events as well.

There may be side effects and discomforts that are not yet known.
Your condition may not get better or may become worse while you are in this study.

What will happen if you get pregnant?
Because of the need for head CT scans, you will have a pregnancy test if you are a female of

childbearing ability. If you become pregnant (or suspect pregnancy) before this study is complete, you must inform the study doctor. You may not take part in this study if you are pregnant or nursing. This research may hurt an embryo or fetus in ways we do not currently know. We will ask you to participate in the follow-up visits but you will not have a CT scan while you are pregnant.

What if there are new findings?
During this study, you will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

Are there benefits to being in the study?
The study drug may improve your recovery from your stroke, however this cannot be guaranteed. Your taking part in this study may help others in the future.

Will it cost you anything to be in this study?
The study drug will be provided to you free of charge.

Procedures that are done only for the study, such as extra lab tests will not be billed to you or your insurance company.

You or your insurance company may be billed for any standard medical care given during this research study.

Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include the costs of treating side effects. Otherwise, you might have unexpected expenses from being in this study.

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

Compensation for Injury
You will be responsible for payment of any treatment or hospitalization you require if you are injured as a result of being in the study. At your request**,** your insurance company will be billed for payment of any treatment or hospitalization. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study.

By signing this consent form, you have not waived any of the legal rights which you otherwise would have as a subject in a research study.

Will you be paid if you join this study?
You will not be paid to participate in this study.

What are the options if you do not want to be in the study?

If you decide not to join this study, you can receive standard care for your stroke. You do not need to participate in this study to get treated for your stroke. Currently, there are no other medications approved for the removal of blood clots from the ventricles. You do not have to join this study. If you do not join, your care at this hospital will not be affected.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?

The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information gathered for this research about:
  - Physical exams
  - Laboratory, x-ray, and other tests results
- Records about any study drug you received

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who may use and give out information about you?

The study doctor and the study staff will use this information. They may also share certain information with agents for the study doctor who provide technical or administrative support.

Who might get this information?

For regulatory purposes, the sponsor of this study is Dr. Daniel F. Hanley, a neurologist and the director of the Brain Injury Outcomes Division at the Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr. Hanley is coordinating this study on behalf of the doctors and staff at approximately 40 other hospitals and academic centers in the U.S. and Europe, including your doctor and hospital. He is assisted by a number of organizations and individuals who provide services in support of this trial. The term "sponsor" includes:

- Dr. Hanley;
- His staff at the Johns Hopkins University; and
- The other people and organizations that assist Dr. Hanley with this study.

Your information may be given to:

- The sponsor;
- The U.S. Food and Drug Administration (FDA);
- Department of Health and Human Services (DHHS) agencies;
- Governmental agencies in other countries;

- Governmental agencies to whom certain diseases (reportable diseases) must be reported;
- Genentech, Inc. (the pharmaceutical company providing the drug for this study);
- The Johns Hopkins University; and
- *[Add local IRB and any additional names here].*

Why will this information be used and/or given to others?

- To do the research,
- To study the results, and
- To see if the research was done right.

The doctors and scientists participating in this study intend to use the information to write medical papers and make presentations at annual meetings. Your identity will not be disclosed in these presentations and publications.

The people working on this study will collect information about you. This includes things learned from the procedures described in this consent form. They may collect other information including your name, address, date of birth, and other details. The research team will need to see your information. Sometimes other people at [YOUR INSTITUTION] may see or give out your information. These include people who review the research studies, their staff, lawyers, or other [YOUR INSTITUTION] staff.

People outside of [YOUR INSTITUTION] may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study, and companies that support the study.

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. Information, which may include copies of your medical records, will be delivered by mail, courier, fax transmission, e-mail attachment, or by submission to a secure website.

Release of your records is necessary for you to participate in this investigational study. If you do not wish to participate, you will still receive full standard medical care.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Use the following Confidentiality section instead of the above Authorization section if the site is not *a covered entity under HIPAA or if the site* is *using a separate HIPAA authorization form.*

Confidentiality

Study information collected about you will be given to the sponsor.

For regulatory purposes, the sponsor of this trial is Dr. Daniel F. Hanley, a neurologist and the director of the Brain Injury Outcomes Program at the Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr. Hanley is coordinating this trial on behalf of the doctors and staff at approximately 40 other hospitals and academic centers in the U.S. and Europe, including your doctor and hospital. He is assisted by a number of organizations and individuals who provide services in support of this trial. The term "sponsor" includes:

- Dr. Hanley;
- his staff at Johns Hopkins; and
- the other people and organizations that assist Dr. Hanley with this study.

It will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study drug may be considered for approval.

Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- The sponsor;
- The U.S. Food and Drug Administration (FDA);
- Department of Health and Human Services (DHHS) agencies;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Genentech, Inc. (the pharmaceutical company providing the drug for this study);
- Johns Hopkins University; and
- *[Add local IRB and any additional names here].*

The people working on this study will collect information about you. This includes things learned from the procedures described in this consent form. They may collect other information including your name, address, date of birth, and other details. The research team will need to see your information. Sometimes

other people at [YOUR INSTITUTION] may see or give out your information. These include people who review the research studies, their staff, lawyers, or other [YOUR INSTITUTION] staff.

The doctors and scientists participating in this study intend to use the information to write medical papers and make presentations at annual meetings. Your identity will not be disclosed in these presentations and publications.

People outside of [YOUR INSTITUTION] may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study, and companies that support the study.

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. Information, which may include copies of your medical records, will be delivered by mail, courier, fax transmission, e-mail attachment or by submission to a secure website.

Release of your records is necessary for you to participate in this investigational study. If you do not wish to participate, you will still receive full routine medical care.

Can you leave the study early?

1. You can agree to be in the study now and change your mind later.
2. If you wish to stop, please tell us right away.
3. Leaving this study early will not stop you from getting regular medical care at this site.
4. If you leave the study early, Johns Hopkins may use or give out your health information that it already has if the information is needed for this study or any follow-up activities.

What could make us take you out of the study early?

The study doctor or the sponsor may stop your participation in this study at any time without your consent for any of the following reasons:

- it is in your best interest;
- You do not later consent to any future changes that may be made in the study plan; or
- For any other reason.

If you leave the study before the planned final visit, you may be asked by the study doctor to have some of the end-of-study procedures done.

What is the source of funding for the study?

The U.S. National Institutes of Health (NIH) is providing the primary funding for this study.

Questions

Contact [NAME] at [NUMBERS} for any of the following reasons:

- If you have any questions about this study or your part in it,
- If you feel you have had a research-related injury or a bad reaction to the study drug, or

- If you have questions, concerns, or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

[YOUR LOCAL IRB/EC NAME AND ADDRESS]

The IRB/EC is a group of people who independently review research.

The IRB/EC will not be able to answer some types of questions, such as questions about appointment times. You may contact the IRB/EC if you cannot reach the research team or if you want to talk to someone else.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers.

Consent

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not given up any of my legal rights.

Consent and Assent Instructions:

Consent: Subjects able to provide consent must sign on the subject line below

Consent is provided by the Legally Authorized Representative for adult subjects unable to consent

Assent: Is required for adult subjects able to provide assent

_____
Printed Name of Subject

_____
Subject's Signature Date/Time

OR

_____
Signature of Legally Authorized Representative Date/Time

_____

Authority of Subject's Legally Authorized Representative or Relationship to Subject

_____

Signature of Person Conducting Informed Consent Discussion Date/Time

_____

Witness to Consent Procedures Date/Time

ASSENT SIGNATURES, For Adult Subjects with a Legally Authorized Representative:

Assent:
For subjects who have a legally authorized representative, I confirm that:

☐ I have explained the study to the extent compatible with the subject's understanding, and the subject has agreed to be in the study.

OR

☐ The subject is not able to assent due to lack of mental capacity.

_____

Signature of Person Conducting Assent Discussion Date/Time

Appendix 4: Sample informed consent form for videotaping a proxy during the modified Rankin Scale interview.

CLEAR III Proxy Videotaping Consent

The purpose of this document is to obtain your consent to talk with you on videotape

1. In the CLEAR III study, we record each patient at three follow-up visits
2. Today, we are unable to record an interview with the patient who is enrolled in the CLEAR III study but too ill to speak
3. We would like to record you instead while you briefly describe the patient's condition
4. The purpose of the recording is to have the same central readers at the University of Glasgow evaluate every patient's condition
5. Only physicians and staff at the University of Glasgow will see the video in a professional hospital research setting
6. The recording will not be broadcast or used for any other purpose and no other copies will be made
7. The recording may be stored on a computer server for 2 years after the end of the study

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Videotape Consent

I, the undersigned, hereby give my permission to be videotaped for the purposes described above.

Name: _____

Signature: _____

Relationship to study patient: _____

Date: _____

Signature/role of CLEAR III interviewer: _____

Date: _____

Appendix 5. Genentech Drug Safety: Safety Reporting FAX Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Version 1 31-May-2012