NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

NIH StrokeNet National Meeting

September 16, 2022

MUSC

MEDICAL UNIVERSITY of SOUTH CAROLINA

NIH

Funded by a grant from the National Institutes of Health

UNIVERSITY OF Cincinnati

Current Status

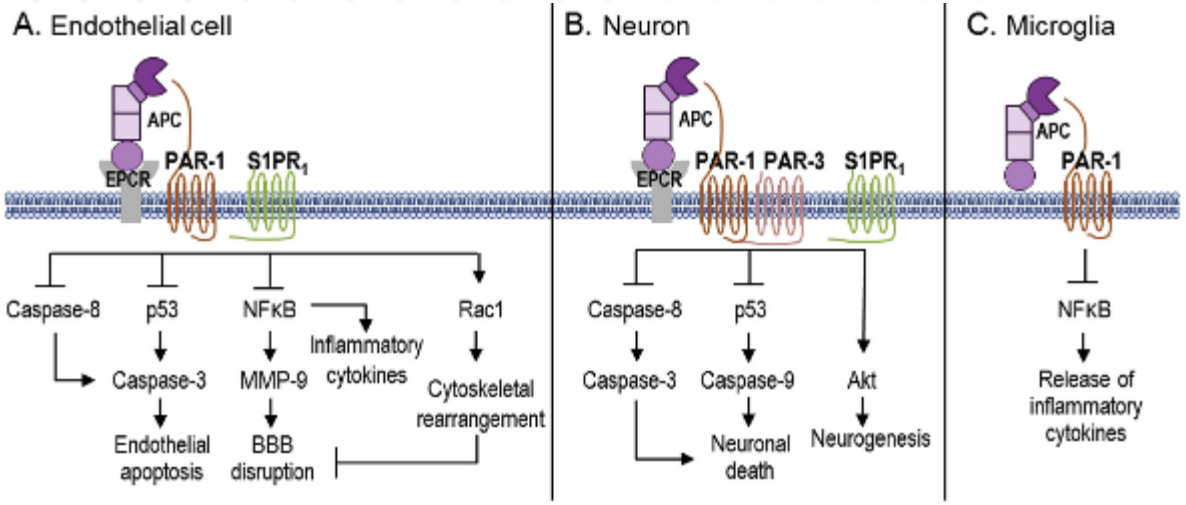
- eNOA awarded June 1, 2022
- All Sub-awards executed
- Now on ClinicalTrials.gov (NCT05484154)
- Protocol modification submitted to FDA 8/18/22 (30-day wait period ends 9/19/22)
- Protocol/consent modification approved by Advarra on 9/8/22.
- DSMB will review the protocol in the very near future
- Regulatory packet (Protocol, consent, payment schedule, CTA) to be sent by 10/3/22 (pending FDA and DSMB review of protocol modification)
- Continuing Review approved 9/1/22

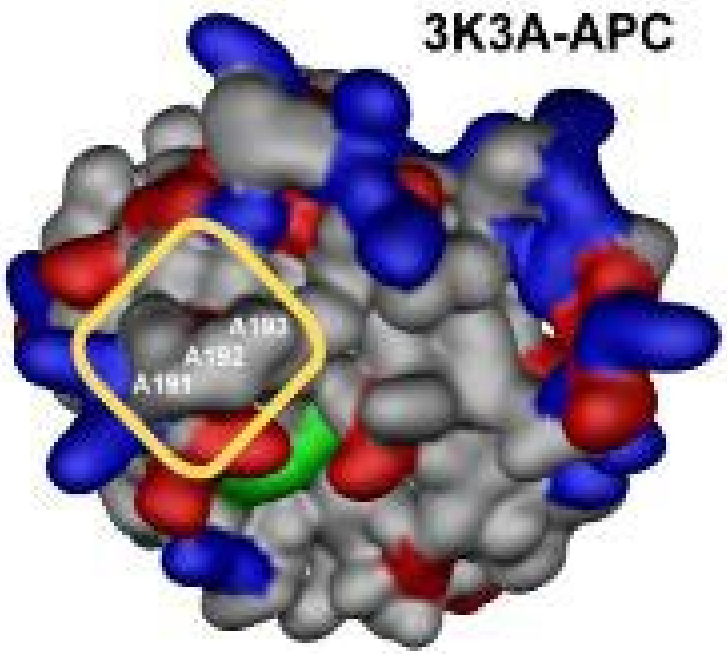
Current Status cont.

- Investigator Meeting to be scheduled as soon as drug delivery date confirmed
- Site Readiness calls to be held in Feb/March
- 3K3A-APC expected to be ready to ship Spring 2023

3K3A-APC: Multiple-action multiple-target approach

- **Endothelium:** Vasculoprotective, Stabilizes BBB integrity
- **Neurons:** Direct Neuronal Protective + promotes neurogenesis
- **Microglia:** Anti-inflammatory
- **Anticoagulant activity:** lowered by >90%





Griffin. Zlokovic, Mosnier, Blood 2018
Amar, …Griffin, Zlokovic, Neuropharmacology, 2018

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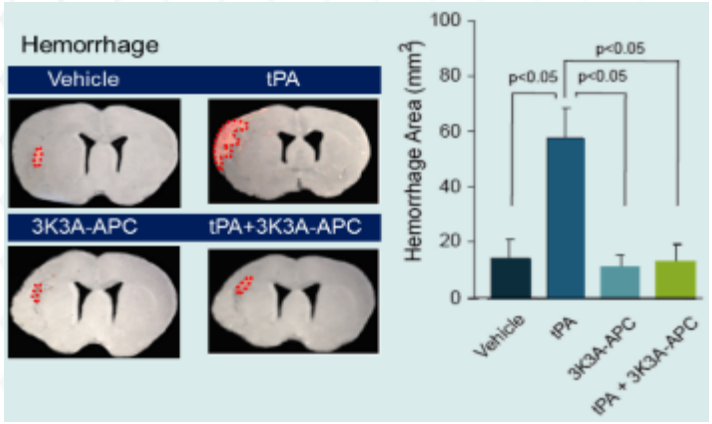
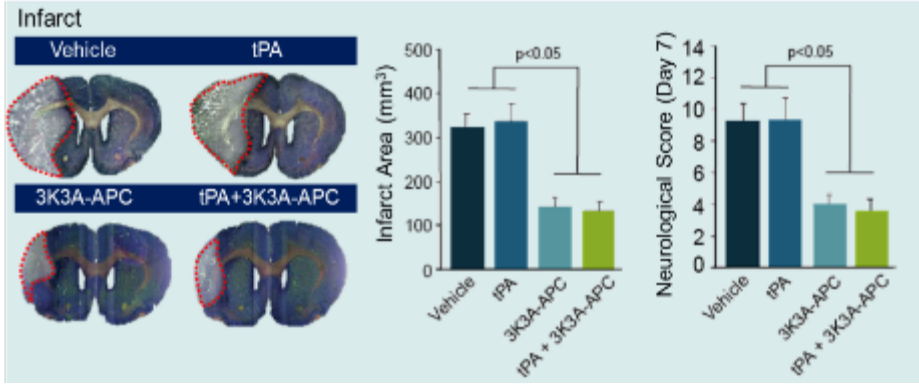
Preclinical data: 3K3A-APC Reduces tPA bleeding



Functional Outcome after Embolic Stroke in Rats



Wang et al., Stroke 2013

THERAPEUTIC WINDOW AFTER STROKE IN RODENTS

3K3A-APC	**12 h**
rtPA	**3-4 h**

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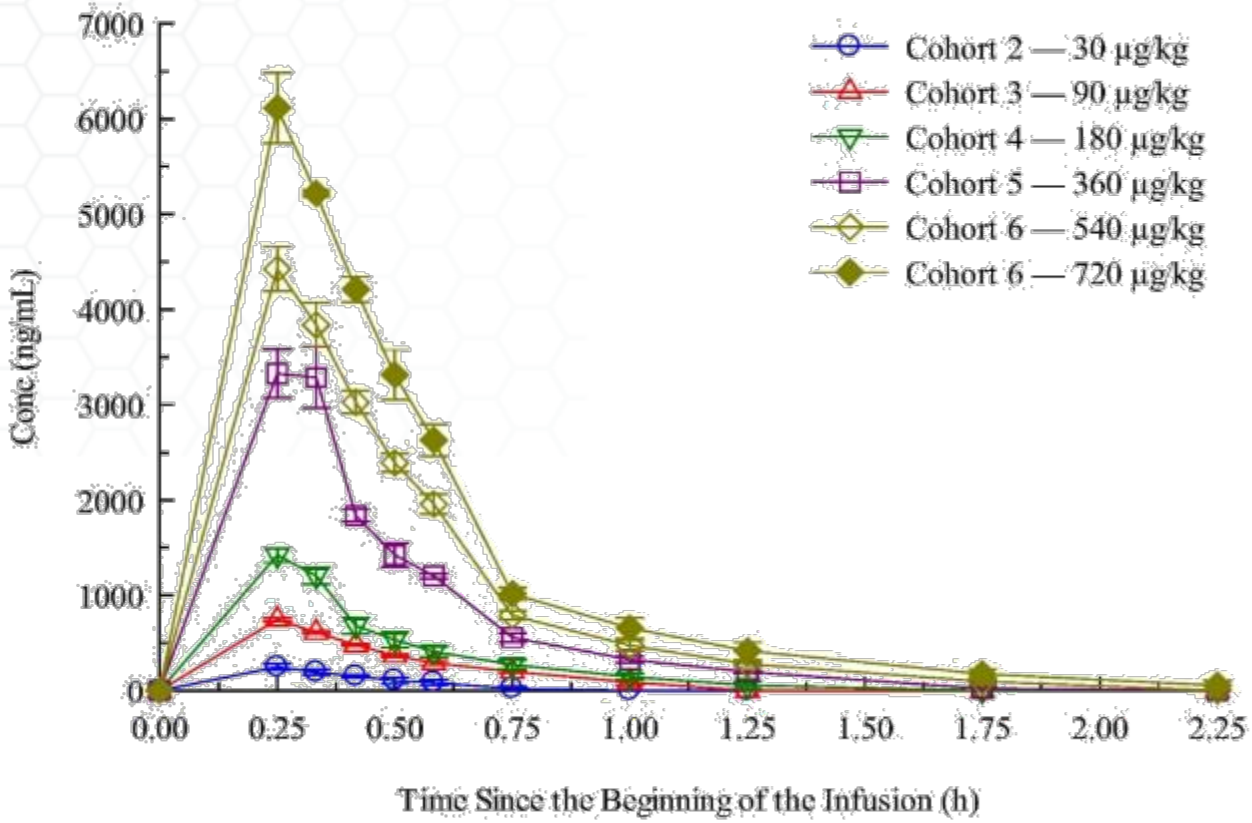
Phase 1 study

3K3A-APC has demonstrated favorable safety and pharmacokinetics



Key Results:

- ✓ ***3K3A-APC exhibits linear PK***
- ✓ ***Drug is safe and well-tolerated in healthy human volunteers – no reported SAEs for 3K3A-APC at any dose level***
- ✓ ***All reported AEs were mild or moderate***

Source: Lyden et al, Zlokovic. Curr Pharm Des 2013

Phase 2 study

NN104 (RHAPSODY): Fewer Asymptomatic Intracerebral Hemorrhage (ICH)

Treatment-Related AE and Hemorrhage	120 (N=15)	240 (N=24)	360 (N=12)	540 (N=15)	All 3K3A-APC (N=66)	Placebo (N=44)	P-value
Any Treatment-Related AE	5 (33%)	12 (50%)	4 (33%)	5 (33%)	26 (39%)	21 (48%)	0.43
Asymptomatic ICH	1 (7%)	2 (8%)	0 (0%)	1 (7%)	4 (6%)	10 (23%)	0.017
Symptomatic ICH	0 (0%)	3 (12%)	0 (0%)	1 (7%)	4 (6%)	1 (2%)	0.65

Among AEs deemed related to treatment by the blinded attending physician, asymptomatic hemorrhage was significantly reduced on drug vs. placebo

Lyden et al…. Zlokovic, Annals Neurology, 2019

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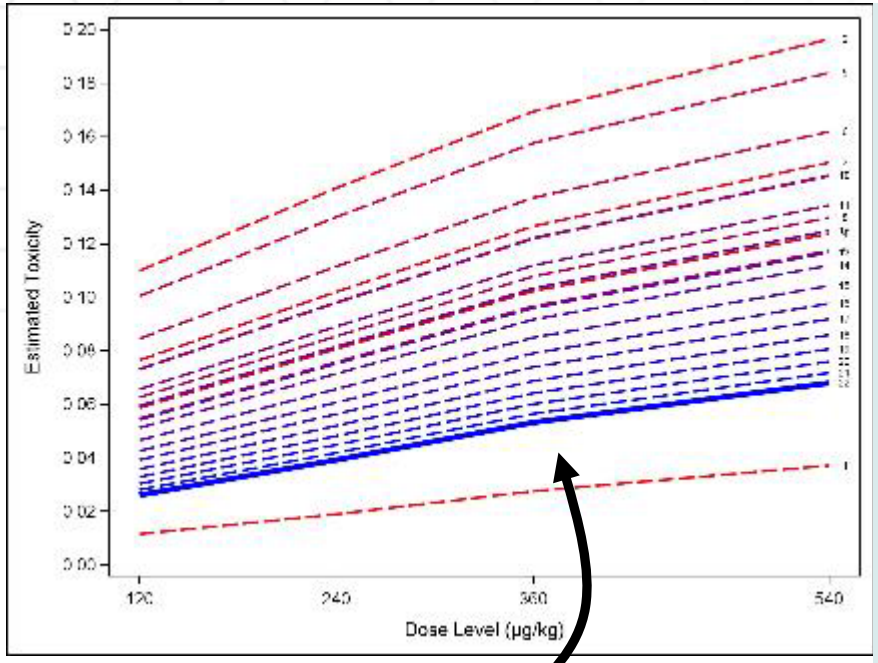
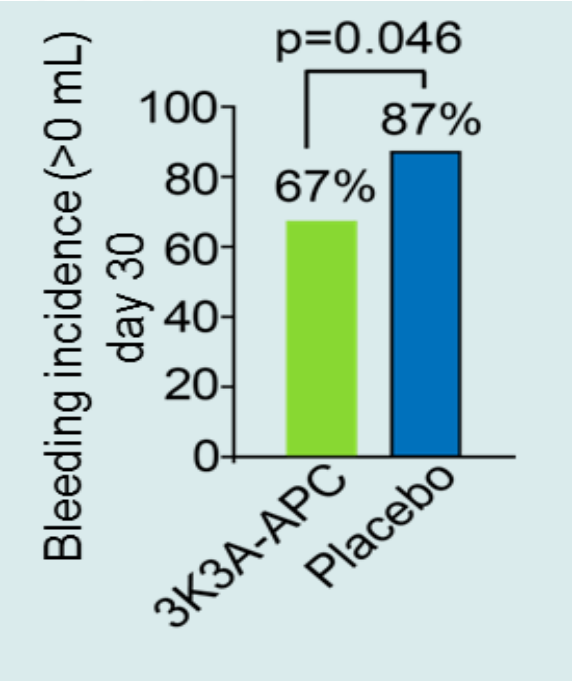
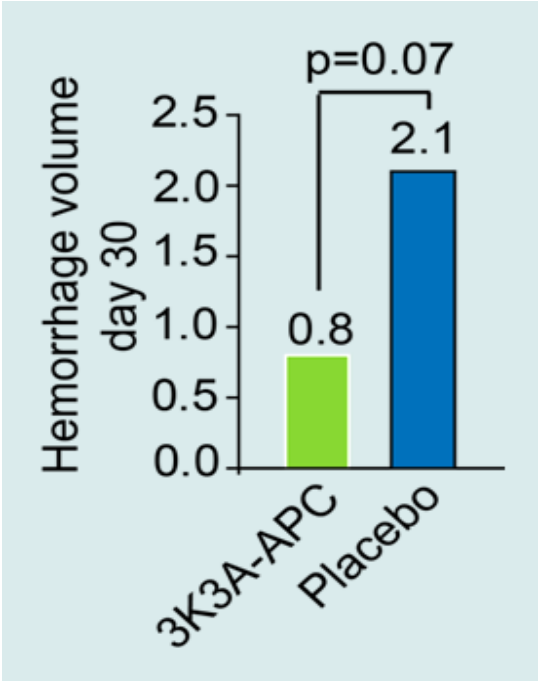
Phase 2 study

3K3A-APC IS SAFE AND REDUCES HEMORRHAGE (MRI) AFTER TPA/THROMBECTOMY







540 µg/kg** is the maximum tolerated dose, with an estimated DLT rate around **7%

Lyden et al…. Zlokovic, Annals Neurology, 2019

Overall Conclusions of Phase 2 Study

- 3K3A-APC appears safe & tolerable
- 540 µg/kg was maximum tolerated dose considered in this study
- A suggestion of vasculoprotection (reduced hemorrhage) requires confirmation in a larger trial

Phase 3 study: RHAPSODY-2

- Study will be conducted in 2 Phases
  - **Lead-in Dosing Finding Phase**: 10 mg, 15 mg, or 30 mg dose (approximately 360 participants)

    Lead-in ends when:

    -All doses fail (trial stops), OR

    -One dose proves superior, OR

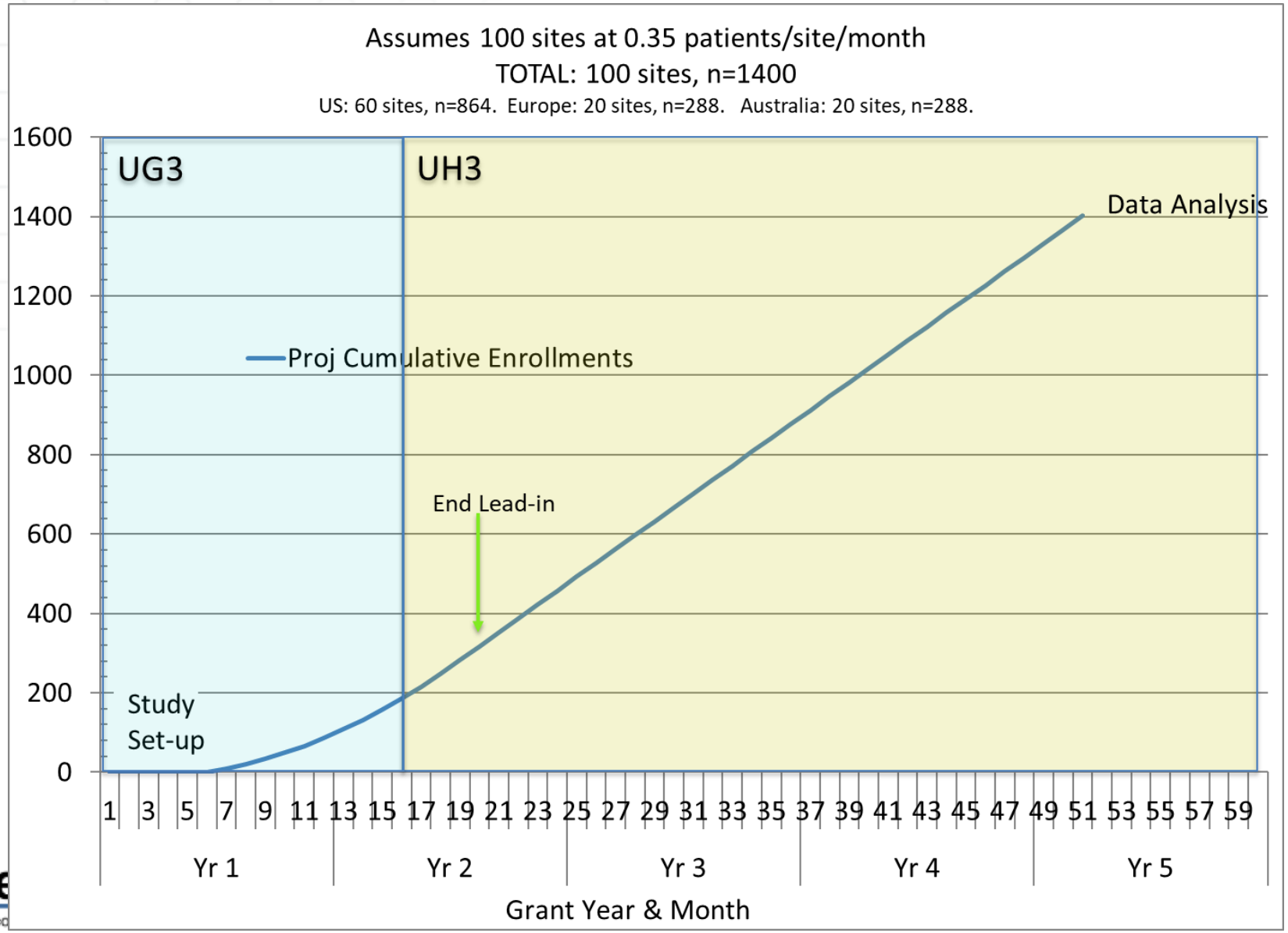
    -If all doses superior, stop at 360 patients and transition to definitive phase with the lowest dose

  - **Definitive phase**

Phase 3 study: RHAPSODY-2 design

Objective		Endpoint	Analyses
Primary:			
- Lead-in:	To evaluate the effect of 3K3A-APC on bleed-free survival at Day 30	Intracerebral bleeding (any blood detected on SWI-MRI) or death at 30 days after ischemic stroke	Bayesian adaptive analysis of posterior probabilities that the proportion of bleeding or death for best dose is lower than control
- Definitive:	To evaluate the effect of 3K3A-APC on 90-day disability	Day 90 mRS	Day 90 mRS scores will be compared between groups using Bayesian ordinal (shift) analysis
Key secondary-Definitive:	To evaluate the effect of 3K3A-APC on bleed-free survival at Day 30	Intracerebral bleeding (any blood detected on SWI-MRI) or death at 30 days after ischemic stroke	Comparison of the proportion of intracerebral bleeding or death at 30 days for the selected dose of 3K3A-APC versus control, using Fisher's exact test

Planned Recruitment



Schedule of Assessments

Procedure	Baseline	Day 1	Day 2	Day 3	Day 4-6	Day 7/Discharge [a] ±3 days	Day 30 ±5 days	Day 60 [b] ±5 days	Day 90 ±10 days
Thrombolysis administration and/or mechanical thrombectomy [c]	SOC								
Inclusion/exclusion criteria	X								
Informed consent [d]	X								
History & physical examination	SOC								
Weight	SOC								
Hematology [e]	SOC					SOC			
Serum chemistry [f]	SOC					SOC			
Coagulation studies [g]	SOC					SOC			
Pregnancy test [h]	X								
Brain imaging (CT or MRI) [i]	SOC								
Vital signs	SOC								
NIHSS[k]	X[j]					X	X		X
Modified Rankin Scale [l]	X						X	X	X
Study drug administration [m]		X	X	X					
AE/SAE assessment [n,o]		X	X	X	X	X	X[o] SAEs only	X	X
Concomitant medications [p]	X		X[p]		X	X	X[o]		
Blood sample for PK analysis [q]			X [q]						
Blood sample for antibody testing [r]	X					X			X
Research MRI brain imaging [s]							X		X
Barthel Index							X		X
Quality of life evaluation (EQ-5D-5L)									X
Depression and suicidality screening [t]							X	X	X
End of study									X

Payment Schedule

SITE START UP PAYMENTS

- start-up $3,500.00

- SUBJECTS ENROLLED AND ALL REQUIRED FOLLOW-UP VISITS COMPLETED
  - Maximum per subject payment is $8,500 total.
  - Payment 1: $3,500 - Issued after Day-30
  - Payment 2: $2,000 - Issued after Day-90 - .
- PROTOCOL COMPLIANCE PAYMENTS
  - $1000 Receipt of all required blood specimens at USC
  - $1000 Receipt of all required MRI images uploaded to the digital archive
  - $1000 Documentation of the 90-day mRS within the protocol window in WebDCU™

Recruitment Costs-Aligning with MOST trial

- $ 5,000 additional payment for 2 patients enrolled w/I 60 days (2 RHAPSODY, or 1 RHAPSODY 1 MOST)
- $1,500 additional payment for after hours (5p-7a) /weekend enrollment

Key Differences between RHAPSODY-2 and MOST Incl/Excl

RECANALIZATION TREATMENT

In MOST, t-PA or TNK must be within 3 hours from last known well.

In RHAPSODY-2, t-PA, TNK or mechanical thrombectomy can be within 24 hours.

DRUG INITIATION

In MOST must be within 60 min (max 75) of START of thrombolytic

In RHAPSODY-2 must be within 120 min of FINISH of thrombolytic

NIHSS SCORE

In MOST must be ≥ 6 prior to IV thrombolytic

In RHAPSODY-2 must be ≥ 5 at the time of randomization

AGREEMENT TO USE EFFECTIVE BIRTH CONTROL THROUGHOUT THE STUDY

In MOST, not a requirement

In RHAPSODY-2, is a requirement

Key Differences between RHAPSODY-2 and MOST Incl/Excl

RAPID AND SIGNIFICANT SPONTANEOUS IMPROVEMENT OF NEUROLOGICAL SIGNS DURING SCREENING

In MOST, not an exclusion

In RHAPSODY-2, is an exclusion

BASELINE mRS

In MOST, exclusion if mRS >3

In RHAPSODY-2, exclusion if mRS ≥ 2

PT

In MOST, PTT above local laboratory limit of normal and INR >1.5 are exclusions

In RHAPSODY-2, prolonged PT (international normalized ratio > 1.7) is an exclusion

Key Differences between RHAPSODY-2 and MOST Incl/Excl

USE OF HEPARIN PRIOR TO ENROLLMENT

In MOST, low molecular weight heparins within the previous 24 hours are an exclusion. In the first 24 hours after t-PA, only heparinized saline line flushes are allowed.

In RHAPSODY-2, use of heparin within the 48 hours prior to enrollment is an exclusion, except to maintain catheter patency. Heparin use after enrollment is allowed during thrombectomy. Prior to or following enrollment, heparin or low-molecular weight heparin used subcutaneously to prevent deep venous thrombosis in hospitalized subjects is allowed.

BLOOD PRESSURE

In MOST, exclusion if SBP >180mmHg and DBP >105mmHg persistently despite antihypertensive intervention

In RHAPSODY-2, exclusion if SBP > 185 mm Hg or < 90 mm Hg and DBP > 110 mm Hg as measured by ≥2 consecutive supine measurements 10 minutes apart, that does not respond to simple treatment (eg, 1 dose of labetalol or nicardipine infusion)

Key Differences between RHAPSODY-2 and MOST Incl/Excl

WEIGHT

In MOST, no specific requirement

In RHAPSODY-2, exclusion if weight > 130 kg

MRI

In MOST, no specific requirement

In RHAPSODY-2, must be able to undergo MRI per local guidelines

CURRENT ABUSE OF ALCOHOL OR ILLICIT DRUGS

In MOST, no specific requirement

In RHAPSODY-2, is an exclusion

RECEIVED PREVIOUS TREATMENT WITH AN INVESTIGATIONAL DRUG OR DEVICE

In MOST, current participation in another research drug treatment or interventional device trial.

In RHAPSODY-2, exclusion if within 30 days prior to enrollment

Key Differences between RHAPSODY-2 and MOST Incl/Excl

- **The following are specific exclusions in MOST, but are not specific requirements in RHAPSODY-2, but could fall into the "any other condition" in RHAPSODY-2 Exclusion #6**
- Any surgery, or biopsy of parenchymal organ in the past 30 days
- Trauma with internal injuries or ulcerative wounds in the past 30 days
- Serious systemic hemorrhage in the past 30 days
- Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR >1.5
- Platelets <100,000/mm3
- Hematocrit <25%
- Creatinine > 4 mg/dL
- Ongoing renal dialysis, regardless of creatinine
- Received Factor Xa inhibitors within the past 48 hours
- Received glycoprotein IIb/IIIa inhibitors within the past 14 days

Other Differences between RHAPSODY-2 and MOST

- Study Team and patient blinded to treatment assignment (unblinded pharmacist)
- 5 fifteen-minute infusions Q12 hours

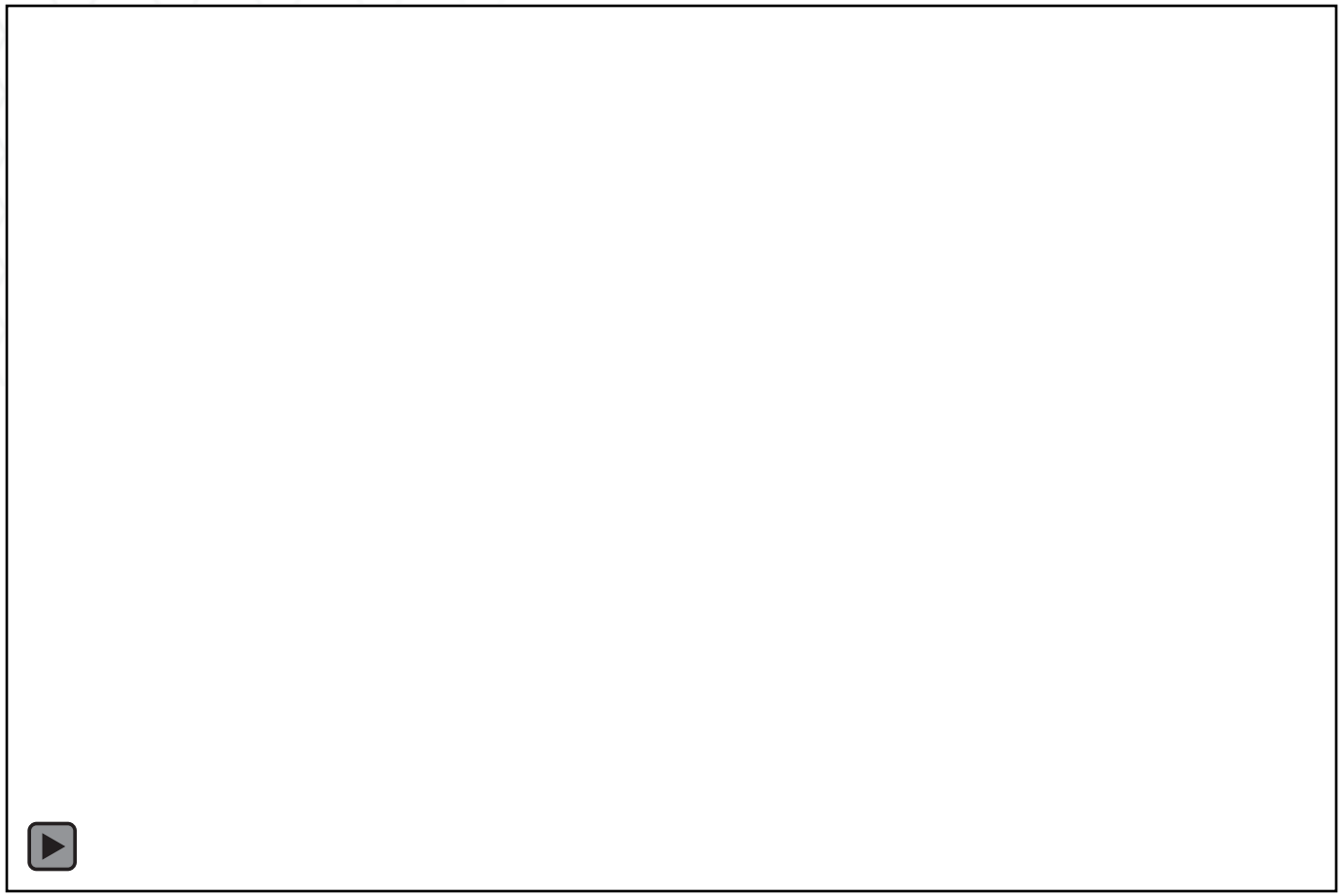
Site Selection

- Currently at 51 Sites
- **RCCs that do not have a participating site**

Mt. Sinai, Stanford University, Univ of Miami, University of California at San Francisco, University of Wisconsin, University of Alabama at Birmingham, and Wake Forest

We are still accepting new sites!

Kent Pryor, PhD CEO ZZ Biotech, LLC



Questions