NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

NIH StrokeNet Coordinator Meeting

July 27, 2022

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

NIH
Funded by a grant from the National Institutes of Health

UNIVERSITY OF Cincinnati

Agenda

- Current status
- RHAPSODY review (3K3A-APC,preclinical, Phase 1 and 2 studies)
- RHAPSODY-2 (study design, schedule of activities, payment schedule, bonus payments)
- Key differences between MOST and RHAPSODY-2
- Site Selection
- Spintech, INC-MRI requirements
- Questions

Current Status *(assumes this is the end of July!)*

- eNOA awarded June 1, 2022
- Sub-awards in-process (UC, MUSC, etc.)
- Protocol/consent revision completed yesterday with modification submission to Advarra next week
- FDA protocol resubmission beginning of August (30-day wait period)
- Drug/Placebo expected to be ready to ship March 2023
- Final site selection currently underway

RHAPSODY-2

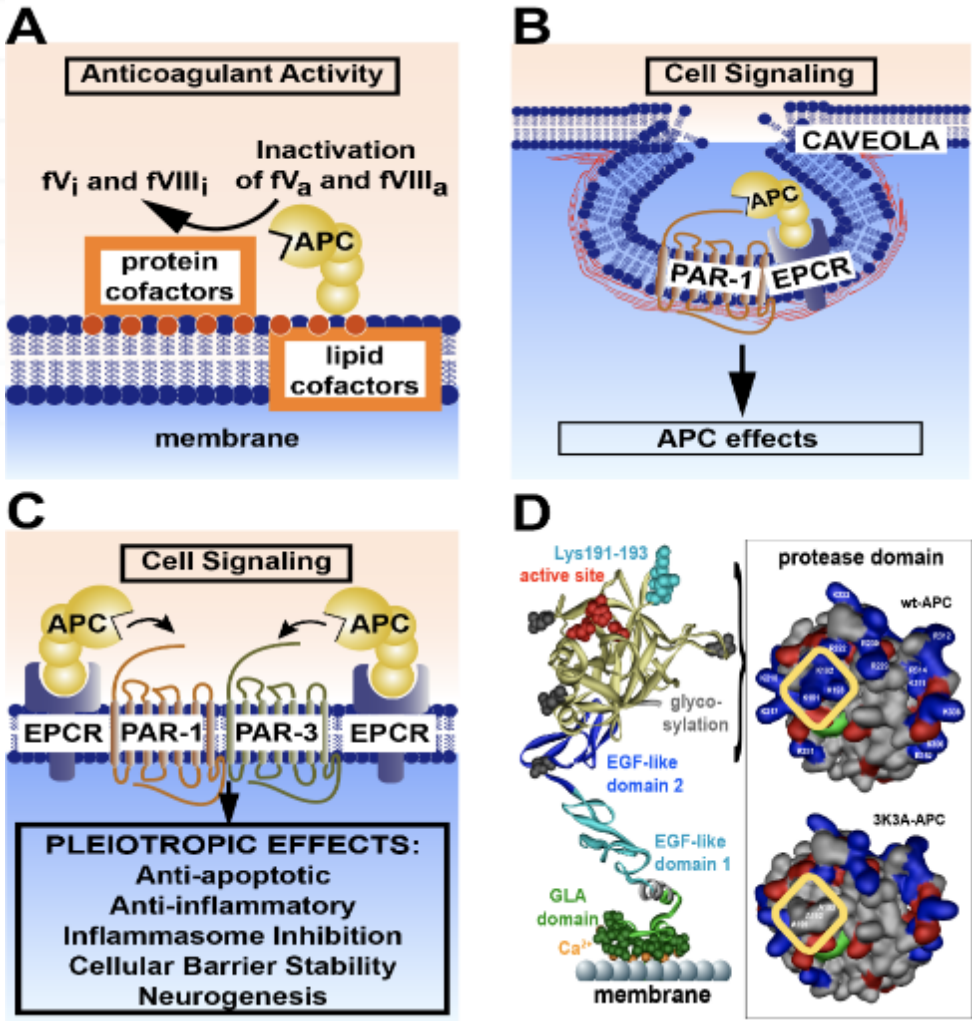
(Recombinant variant of **H**uman **A**ctivated **P**rotein C in combination with tissue pla**S**min**O**gen activator (thrombolysis) in mo**D**eratel**Y** severe acute hemispheric ischemic stroke)

ACTIVATED PROTEIN C(APC): Pathways and the Structure of Signaling-Selective 3K3A-APC

APC, a serine protease and active form of **protein C** produced by the liver

- *Anticoagulant activity*
- *Cell signaling activities*

3K3A-APC, a signaling selective *APC mutant* with 3 Lys residues replaced by Ala residues resulting in **<** ***10%*** of the APC anticoagulant activity, and fully preserved cell signaling activities.



Griffin, Mosnier, Zlokovic, Blood 2018

The polypeptide structure
Gla domain
EGF-like domains

Active site:
- Protease domain
- Multiple domain binding exosites:

✓ *loop 37* KKK191-193 for recognition of Va and VIIIa

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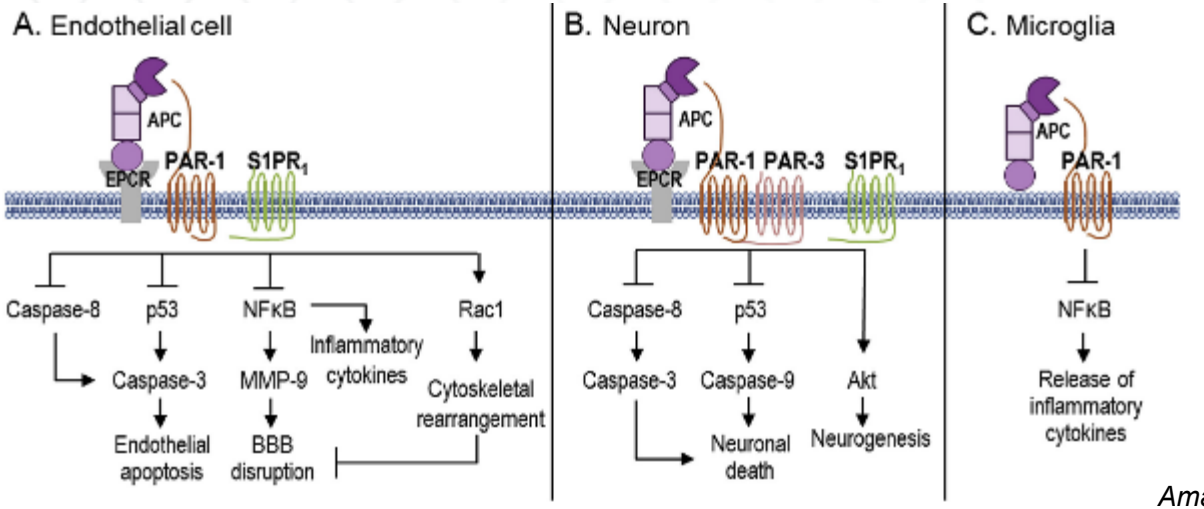
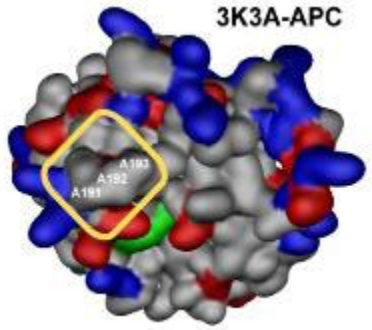
3K3A-APC: Multiple-action multiple-target approach

- **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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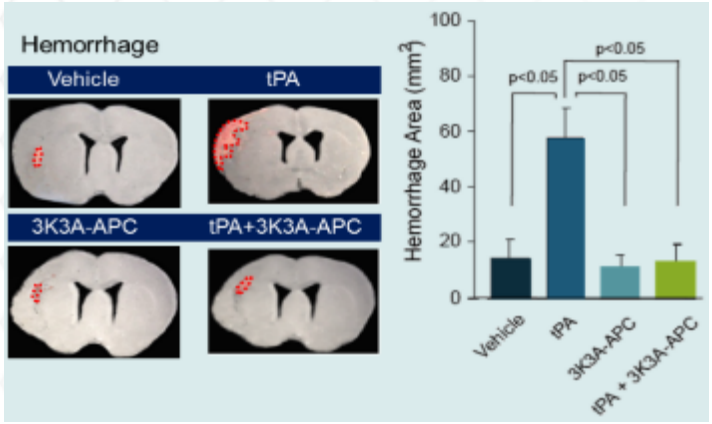
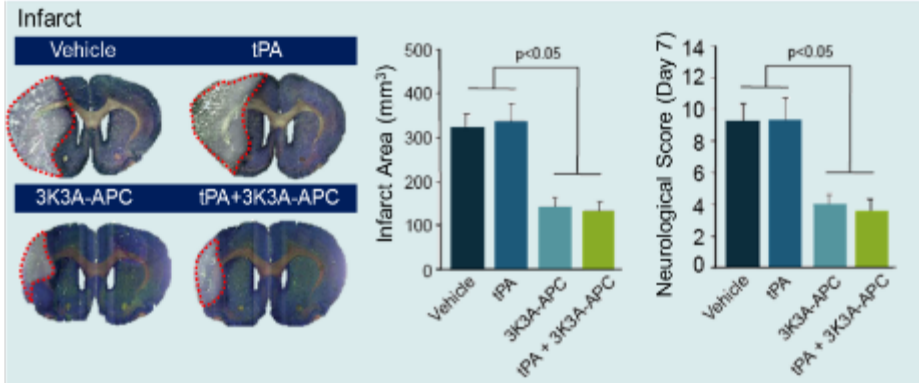
Preclinical data: 3K3A-APC Reduces tPA bleeding



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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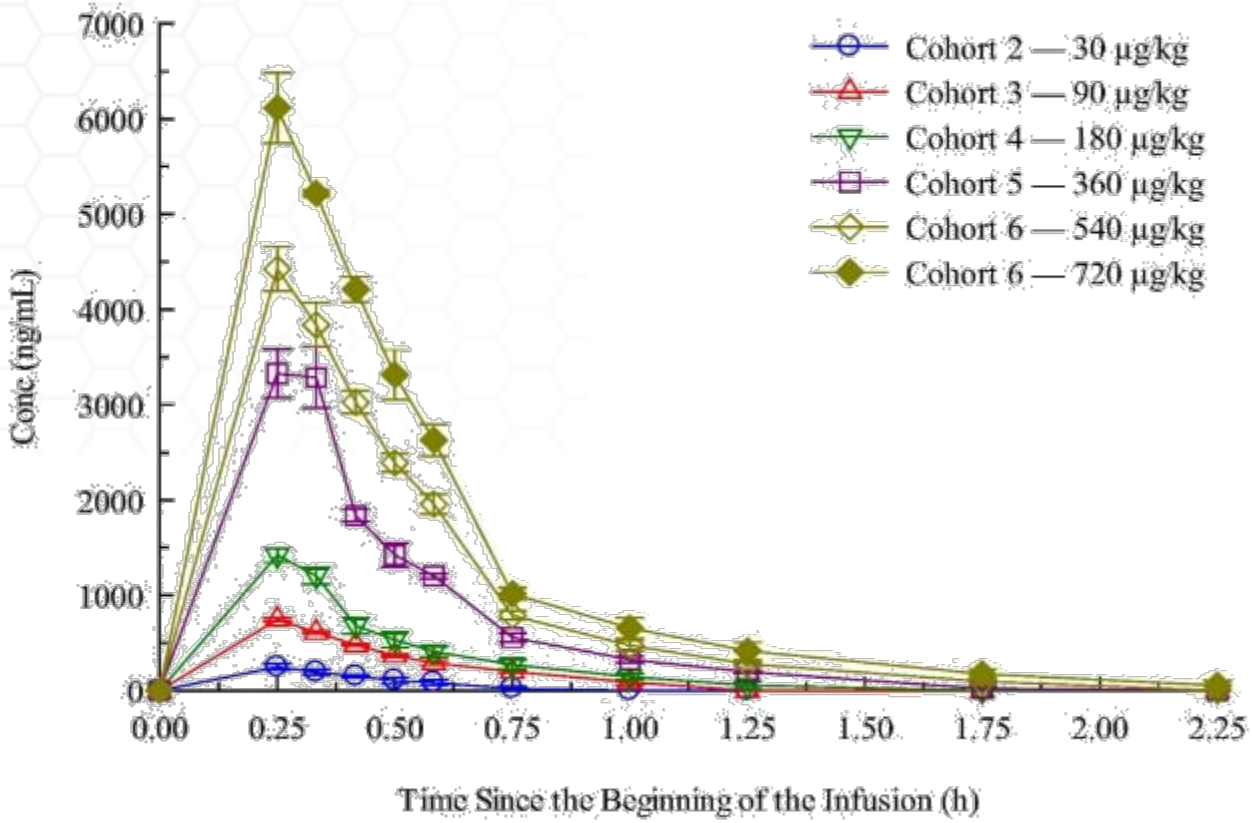
Phase 1 study

3K3A-APC has demonstrated favorable safety and pharmacokinetics



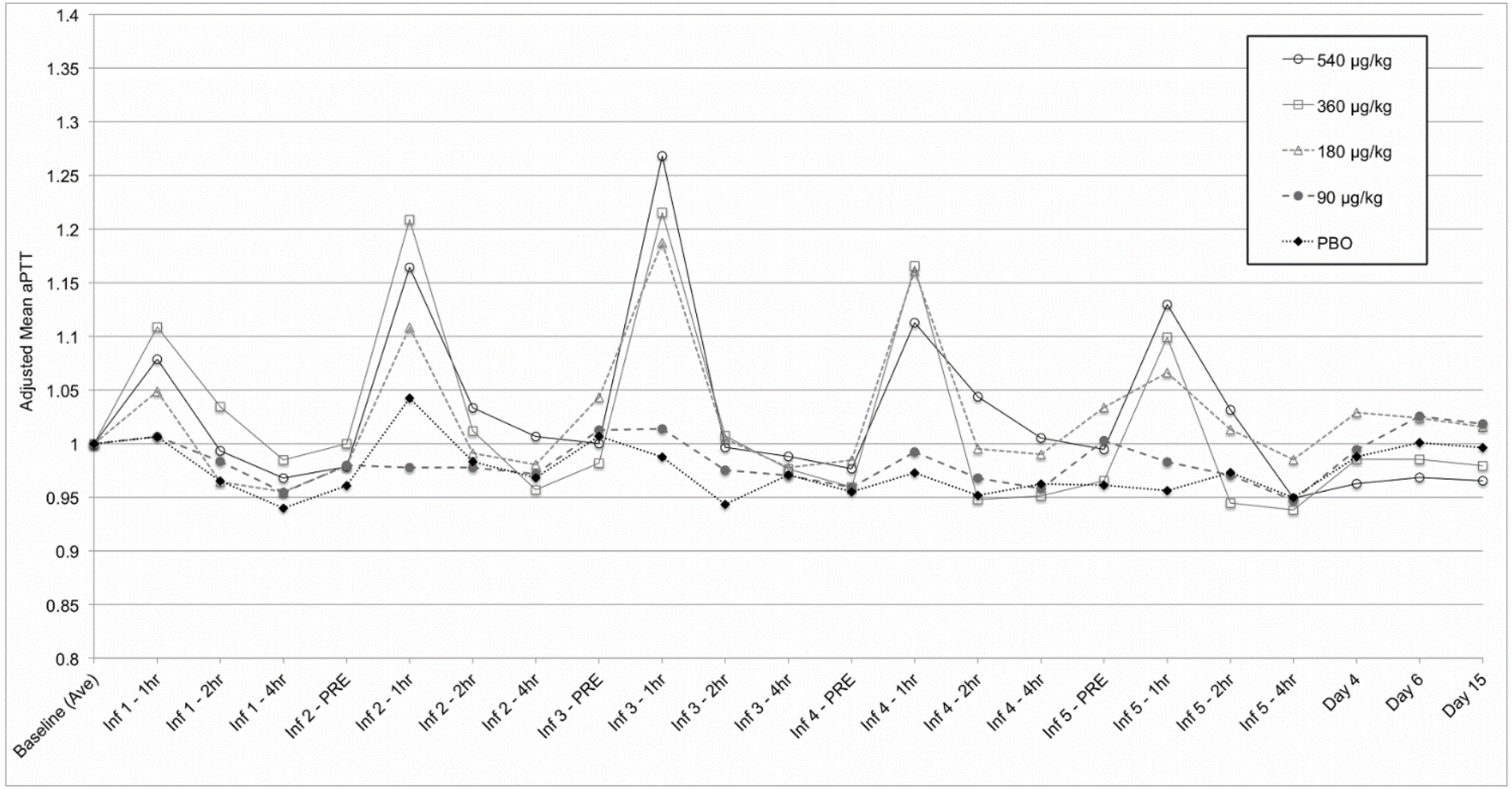
Key Results:

- ✓ ***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 1 study

No individual aPTT exceed 1.51 x ULN at 1 hour following infusion (60.4 sec) aPTT

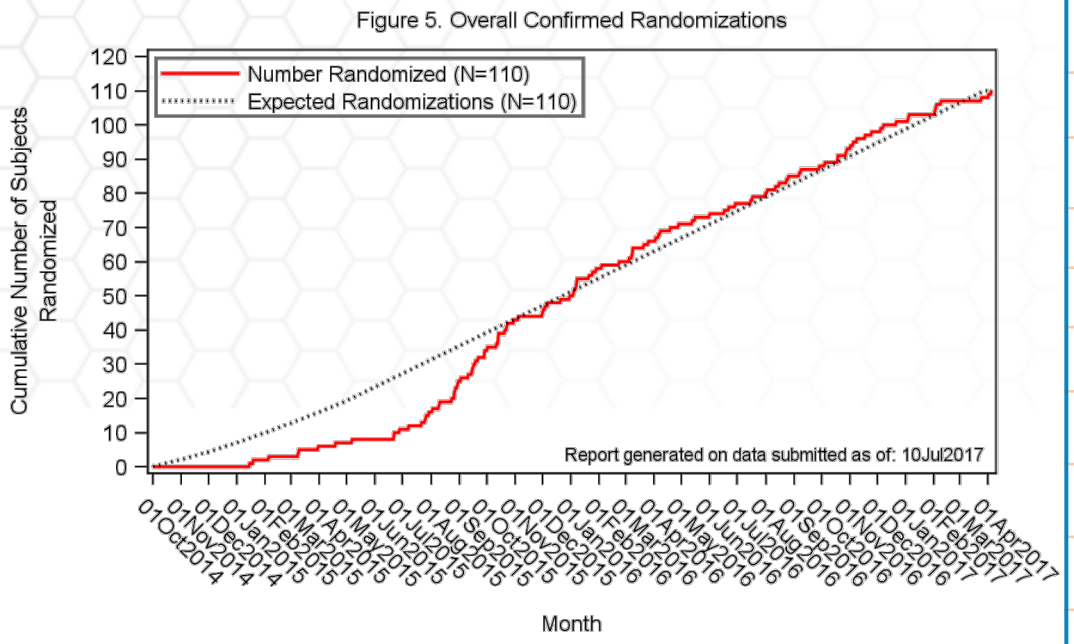


aPTT,
activated partial thromboplastin time

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

Phase 2 study

NN104 (RHAPSODY): Study Enrollment



Demographics			
	Placebo (n = 44)	3K3A-APC (n = 66)	P-value
Males	24 (55%)	29 (44%)	0.33
Caucasian	36 (82%)	52 (79%)	0.80
Hispanic/Latino	7 (16%)	4 (6%)	0.12
Age	64 (12.0)	64 (15.2)	0.95
Years Education	13 (2.5)	13 (3.9)	0.20
Right Hand Preference	36 (82%)	58 (88%)	0.43
Height (cm)	170 (9.9)	169 (10.5)	0.78
Weight (kg)	84 (18.0)	84 (19.1)	0.95
Platelet Count ≥ 100K	42 (96%)	65 (99%)	0.40
History - Diabetes	18 (41%)	18 (27%)	0.15
History - Hypertension	33 (75%)	52 (79%)	0.65

110 subjects enrolled (66 drug, 44 placebo)

Lyden et al…. Zlokovic, Annals Neurology, 2019

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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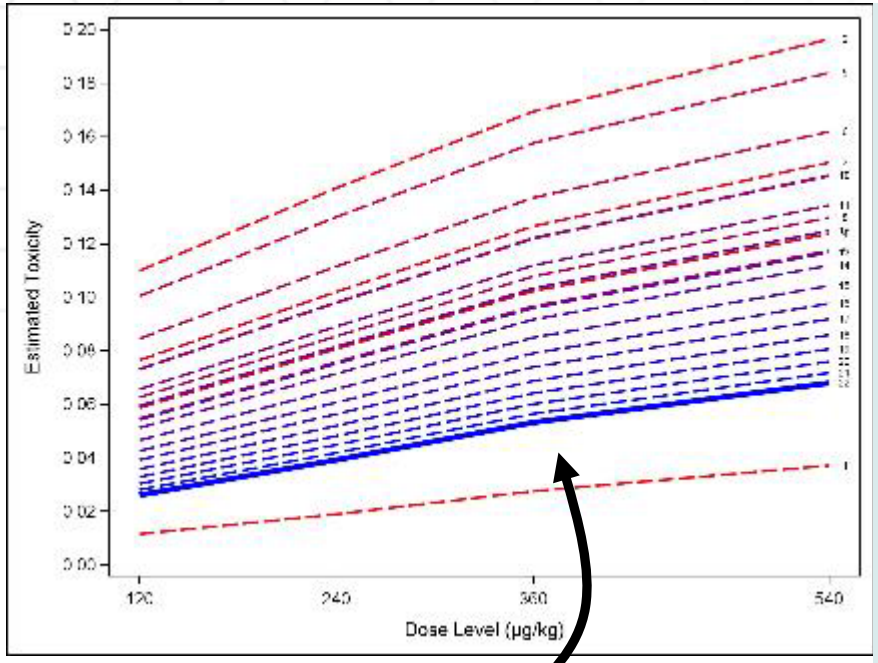
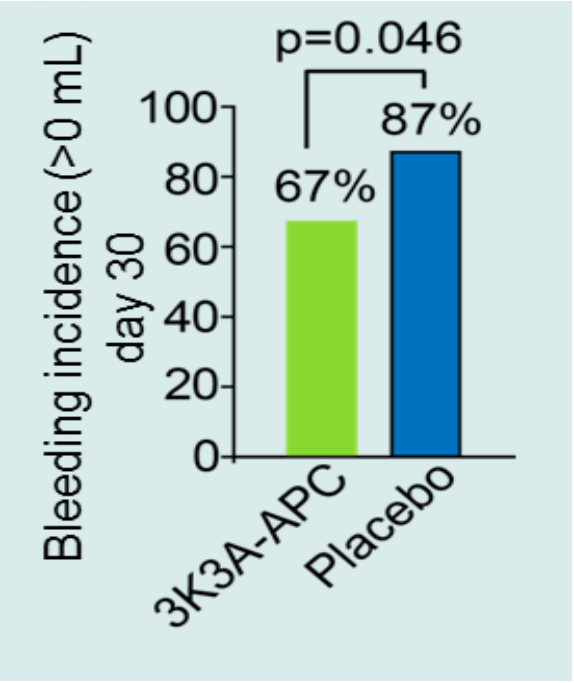
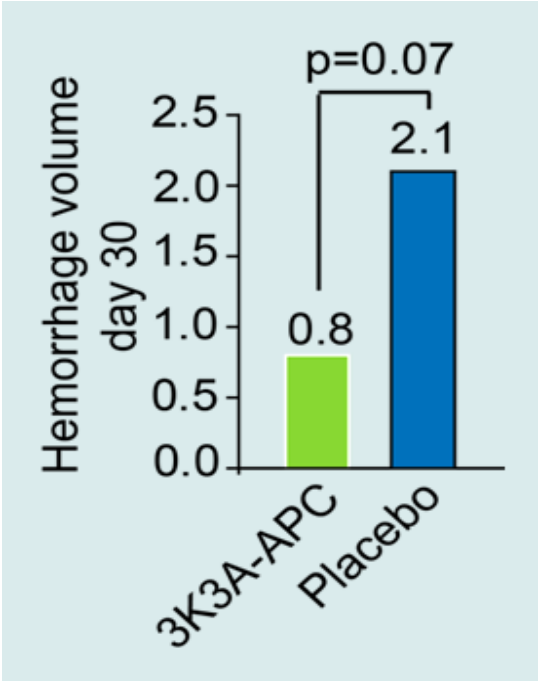
Phase 2 study

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, 15, or 30mg dose (approximately 360 participants)

    Lead-in ends when:

    -All doses fail (trial stops), OR

    -One dose proves superior, OR

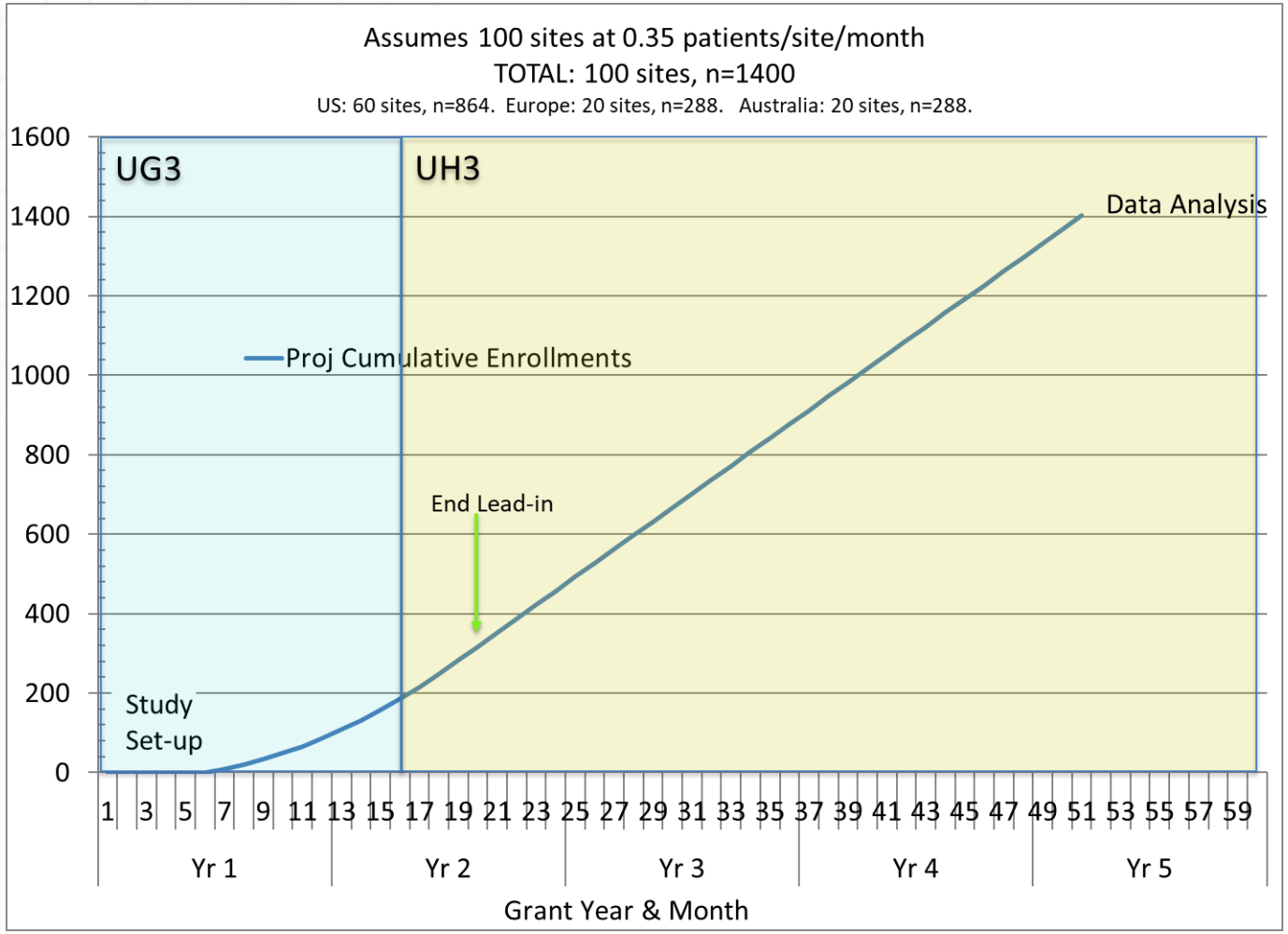
    -If all doses superior, stop at 360 patients and transition to definitive phase with the lowest dose

  - **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



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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

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Key Differences between RHAPSODY 2 and MOST

- Pretty much all stroke except hemorrhagic included
- Pre-stroke mRS ≥ 2
- Qualifying NIHSS ≥ is AFTER tPA/TNK (w/I 30 min of randomization)
- Study drug must be initiated within 120 minutes from tPA/TNK FINISH or arterial puncture (whichever is sooner)
- Study Team and patient blinded to treatment assignment (unblinded pharmacist)
- 5 fifteen-minute infusions Q12 hours
- Research MRI at 30 and 90 days

Site Selection

- Need contact information for all sites that are confirmed to participate now or even if you are still undecided.
- RCC managers please reach out to your satellite sites to make sure that we know of everyone who intends to participate (many sites did not submit a survey)
- Need PI name/email, CRC name/email/phone, Site name

Spintech, INC

Questions