

**STAIR XI Attendees:**

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Project/Trial:

A Randomized, Double-Blind, Placebo-Controlled Proof-of-Concept Study to Assess the Safety and Efficacy of Elezanumab in Acute Ischemic Stroke.

Investigational Product:

Elezanumab

Potential Significance of Product:

Elezanumab is an investigational product under development for improvement of neurologic function in patients with acute ischemic stroke. Treatment of acute ischemic stroke patients with Elezanumab has the potential to accelerate recovery and/or provide more complete recovery by decreasing neuronal damage and enhancing restoration of neuronal activity.

Study Status:

Phase II – enrolling

Sites/Locations:

Approximately 30 sites; US, Canada, Spain

Principal Investigators:

See ClinicalTrials.gov

Product Application:

Elezanumab is a monoclonal antibody of the human immunoglobulin (Ig)G1 isotype that binds selectively to repulsive guidance molecule A (RGMA). Repulsive guidance molecule A is an inhibitor of axonal outgrowth and recognized as an important factor in inhibiting neuronal regeneration and functional recovery following central nervous system (CNS) damage. Elezanumab is being investigated to treat acute ischemic stroke. It is currently in phase 2 study (NCT04309474) for the treatment of acute ischemic stroke.

Additional Comments:

See ClinicalTrials.gov

ALLM



STAIR XI Attendees:

Harry Reddy: harry@allm.net

Company Summary:

Allm is a company dedicated to expanding and extending knowledge among healthcare professionals including stroke researchers and organizations by innovating platforms and tools which allow researchers, clinicians, and their related networks to easily, securely, and reliably collaborate to transfer and share; new data, essential information, and archived knowledge with one another. Allm is currently exploring, and invites your input on, necessary but undeveloped tools and ways to support and amplify the rapidly expanding stroke research and treatment arena.

ARUNA BIOMEDICAL



STAIR XI Attendees:

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Company Statement:

ArunA Biomedical is actively engaged in a number of research and development activities aimed at expanding and improving stroke treatment options.

ASTROCYTE PHARMACEUTICALS INC.



STAIR XI Attendees:

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Investigational Product:

AST-004

Study Status:

Preclinical

Product Application:

Astrocyte Pharmaceuticals is developing AST-004, a stable small molecule therapeutic that targets astrocytes, natural caretaker cells in the brain that are essential and underappreciated regulators of stroke neuropathology. AST-004 enhances the mitochondrial energy production of astrocytes, enhancing multiple healing mechanisms, including protection against edema, glutamate excitotoxicity, and oxidative stress, all important cellular responses occurring in stroke etiology. AST-004 is an agonist of the GPCR adenosine A3 receptor (ADORA3), demonstrating excellent pharmacokinetics and blood-brain barrier permeability in preclinical species.

The neuroprotective efficacy of AST-004 has been demonstrated in a wide range of models including permanent and transient stroke, single vessel mini-stroke and MCAo, and early and late (24 hr.) interventions. In non-human primates (cynomolgus macaque), a 4-hour tMCAO was conducted with a 22-hour steady-state intravenous infusion initiated 2 hours prior to reperfusion (vehicle or four AST-004 dose levels, n=4/group). Stroke lesion, perfusion deficits and penumbral endpoints were assessed at multiple timepoints. AST-004 treatment resulted in statistically significant improvements in outcome relative to vehicle, up to a 44% decrease in lesion volume ($p=0.02$) and a 72% decrease in percentage of lesion growth ($p=0.0006$) over the 5-day study period.

AST-004 is a first-in-class candidate that warrants further evaluation in human clinical stroke trials, as a neuroprotective agent that is complementary to standard of care therapies (i.e., tPA and mechanical thrombectomy) and which is applicable to early and late intervention-time windows. AST-004 is projected to have a 24-hour half-life in humans and be administered as a single 10-minute IV bolus. AST-004 has completed preclinical GLP toxicology studies and demonstrates a broad therapeutic index, and low/ minimal toxicity effects, with no significant drug-drug interactions and as a small molecule, no anticipated interactions with tPA. AST-004 will be starting Phase 1 clinical studies in 2021 and then advance to Phase 2 studies in large vessel occlusion stroke patients IV bolus. AST-004 has completed preclinical GLP toxicology studies and demonstrates a broad therapeutic index, and low/ minimal toxicity effects, with no significant drug-drug interactions and as a small molecule, no anticipated interactions with tPA. AST-004 will be starting Phase 1 clinical studies in 2021 and then advance to Phase 2 studies in large vessel occlusion stroke patients.



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Project/Trial:

Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 (Glibenclamide) for Severe Cerebral Edema Following Large Hemispheric Infarction (CHARM)

Investigational Product:

BIIB093 (IV Glibenclamide)

Study Status:

Phase III study, currently enrolling

Sites/Locations:

Planned recruitment approximately 200 sites in US, Europe, Australia, Belgium, Brazil, Canada, China, Croatia, Czechia, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Korea, Lithuania, Portugal, Russia, Spain, Switzerland, Taiwan, and UK

Principal Investigators:

Co-global study leads:

- Dr. Taylor Kimberly, M.D., Ph.D., Massachusetts General Hospital
- Dr. Kevin Sheth, M.D., Yale

Please see the following link for a complete listing of PIs/hospitals:

<https://www.clinicaltrials.gov/ct2/show/NCT02864953?term=BIIB093&draw=2&rank=2>

Product Application:

The target indication for BIIB093 (IV glibenclamide) is large hemispheric infarction, a severe form of ischemic stroke where cerebral edema often leads to a disproportionately large share of stroke-related morbidity and mortality. In pre-clinical studies, BIIB093 was shown to block SUR1-TRPM4 channels that mediate malignant cerebral edema. Clinical proof-of-concept studies previously showed the potential of BIIB093 to reduce edema, disability, and the risk of death in patients with LHI, supporting further development in later stage studies.

BRAINOMIX



STAIR XI Attendees:

Dr. George Harston, Chief Medical and Innovation Officer at Brainomix; Stroke Physician at Oxford University Hospital NHSFT: gharston@brainomix.com; Twitter: @GeorgeHartson)

Project/Trial:

Multiple ongoing studies. Please contact George Harston for more details.

Investigational Product:

e-Stroke Suite / Brainomix360

Study Status:

Multiple ongoing studies. Please contact for individual details.

Sites/Locations:

Research activity in Europe, Brazil, USA, China

Product Application:

AI-imaging support

Additional Comments:

Brainomix has a **strong academic tradition**, from its origins as a company spun out of the **University of Oxford** through to the integration of the e-Stroke Suite into multiple clinical trials ongoing today. Brainomix was the first company to use AI to support image interpretation in acute stroke and continues to lead innovation in the field.

Brainomix has always prided itself on the **comprehensive nature of its solutions**, but particularly emphasises the opportunity offered by AI imaging support for **augmenting the value of simple imaging** to deliver improved stroke care in **all healthcare settings**. Brainomix current research activity spans highly specialised imaging research through to pragmatic randomised controlled trials and impact evaluation quantifying the real-world impact of AI technology.

Brainomix would be delighted to **explore new research collaborations** using its technologies, connecting user sites, and leveraging the Brainomix in-house AI expertise to deliver the next generation of stroke imaging technology



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Project/Trial:

xImpACT-P - RCT aims to demonstrate that SPG stimulation started within 6 hours from stroke onset slows the expansion of the infarct core volume in acute ischemic stroke.

Investigational Product:

Ischemic Stroke System 500 (ISS-500)

Study Status:

ImpACT-P: Enrolling – temporarily on hold pending COVID-19 situation

Sites/Locations:

4 centers in Georgia

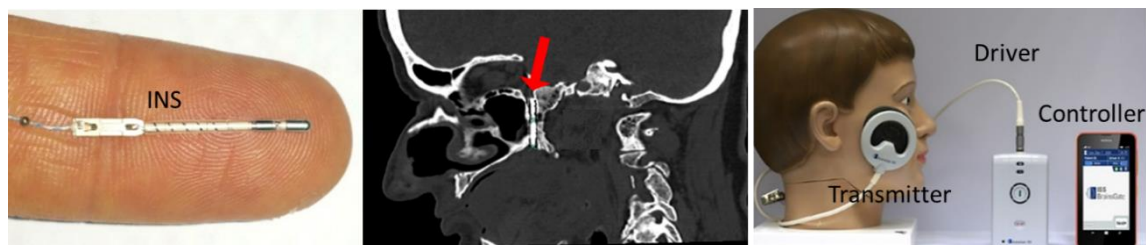
Principal Investigators:

ImpACT-P Steering Committee Chairpersons:

- Prof. Jeffrey Saver, David Geffen School of Medicine, UCLA, Los-Angeles, CA
- Prof. Greg Albers, Stanford University Medical Center, Stanford, CA

Product Application:

A minimal invasive bedside procedure (less than 5 minutes skin to skin) is used to implant the INS neurostimulator in the greater palatine canal. The INS is activated by a Transmitter mounted on the patient's cheek. Treatment is delivered for 4 hours per day over five days, and then the implant is removed.



Additional Comments:

The ISS500 is currently in regulatory review process as a primary treatment in the 8-24 hours window.

ImpACT-P is aimed to demonstrate that SPG stimulation can also serve as a complementing therapy to revascularization, in the hyper acute phase.

CERENOVUS



STAIR XI Attendees:

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Company Statement:

Cerenovus is actively engaged in a number of research and development activities aimed at expanding and improving stroke treatment options.

ceribell

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YouTube: www.youtube.com/channel/UC6aYgiK-q1k7Woes17UQldg

Project/Trial:

STROKE – Suspected Emergent Stroke Detection with EEG

Investigational Product:

Ceribell Rapid Response EEG System

Potential Significance of Product:

Feasibility study to understand the application of EEG in detection, treatment, and management of stroke patients.

Study Status:

Enrolling

Sites/Locations:

Three sites in the USA

Principal Investigators:

Wade Smith, MD, PhD (UCSF)

Anna Finley, MD (Stanford University)

Adam Rizvi, MD (St. Joseph's Crandolet)

Product Application:

Ceribell would like to enable faster and accurate detection of stroke using EEG technology for patients and clinicians.

DIFFUSION PHARMACEUTICALS



STAIR XI Attendees:

Anna Grace, MA, RN, CCRP, Project Manager: agrace@diffusionpharma.com

Project/Trial:

Prehospital Administration of Stroke Therapy – Trans Sodium Crocetinate (PHAST-TSC)

Investigational Product:

Trans Sodium Crocetinate (TSC)

Potential Significance of Product:

TSC is an oxygen diffusion enhancing novel molecule that selectively regulates the movement of oxygen into hypoxic tissues. When added to an aqueous solution such as blood plasma, TSC causes the water molecules to form more hydrogen bonds with each other, leading to a more ordered arrangement of water molecules. Oxygen can more easily diffuse into hypoxic tissue due to the more open structural arrangement.

TSC is being tested as a potential neuroprotectant. The primary objectives of the study are to evaluate the efficacy and safety of field-initiated TSC in improving the long-term functional outcome of subjects with acute stroke.

Study Status:

Phase IIb, enrollment suspended for at least the duration of the pandemic, while the Company focuses its resources on developing TSC for use in treatment of hospitalized COVID-19 patients.

Sites/Locations:

US sites only - Central Virginia and Los Angeles, CA

Principal Investigators:

Jeffrey L Saver (UCLA)
Nerses Sanossian (LAC+USC)
Andrew Southerland (University of Virginia)
Karen Johnston (University of Virginia)

Product Application:

TSC is being investigated in improving clinical outcomes for patients afflicted with life-threatening diseases where cellular oxygen deprivation is a key factor, including patients who have suffered a stroke.

**STAIR XI Attendees:**

Jonathan Birchall, VP Franchise Head/Squad Leader
Michael Liberman, Squad Medical Partner and Medical Team Lead
Barbara Purdon, Principal Medical Science Director, Medical Lead for TIMELESS
John Stephens, Medical Director Lytics
Rachel Garvin, Senior Medical Director, Lytics
Florence Toy, Medical Science Director, Lytics Medical Information
Andrew Weiss, Principal Life Cycle Leader, Lytics

Project/Trial:

TIMELESS, Thrombolysis in **IM**aging Eligible Late window patients to evaluate the **Efficacy** and **Safety** of tenecteplase

Investigational Product:

Tenecteplase or TNKase

Potential Product Significance:

Tenecteplase is a tissue plasminogen activator, similar to alteplase but with 3 major changes in the amino acid chain. These changes lead to increased fibrin specificity, increased resistance to PAI-1 and a longer half-life allowing for bolus administration. Tenecteplase has been shown to open a larger percent of LVOs compared to Alteplase (22% vs 10%) (Campbell, 2018) and may decrease the need for mechanical thrombectomy in this patient population.

Study Status:

TIMELESS is a phase III label-enabling, randomized, placebo-controlled trial that is currently enrolling in the US and Canada. Current expected completion date is June 2022. At present time 200 patients have been enrolled.

Sites/Locations:

We currently have 73 sites which includes both hubs and spokes. The majority of the sites are within the US, there are 2 sites in Canada

Principal Investigators:

Greg Albers, MD – Stanford University

Product Application:

Tenecteplase is currently on the market and is indicated for use in the reduction of mortality associated with acute myocardial infarction (AMI). Treatment should be initiated as soon as possible after the onset of AMI symptoms. The dose for AMI is weight based up to 50mg. Tenecteplase use in AIS is being studied in TIMELESS at the dose of 0.25mg/kg with a maximum of 25 mg in imaging-eligible patients.

ISCHEMIX



STAIR XI Attendees:

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Company Statement:

Ischemix is actively engaged in a number of research and development activities aimed at expanding and improving stroke treatment options.

LUMOSA THERAPEUTICS



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Project/Trial:

LT3001-201

Investigational Product:

LT3001

Study Status:

Phase II, enrolling, expected to be completed by end of 2020

Sites/Locations:

10 sites in US and Taiwan

Principal Investigators:

Thomas Devlin (Chattanooga Center for Neurologic Research, US)
Luther Creed Pettigrew (University of Kentucky, US)
Yousef Hannawi (The Ohio State University Wexner Medical Center, US)
Jawad Kirmani (JFK Neuroscience Institute, US)
Tsong-Hai, Lee (Linkou Chang Gung Memorial Hospital, TW)
Hung-Yu, Huang (China Medical University Hospital, TW)
Po-Lin, Chen (Taichung Veterans General Hospital, TW)
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A-Ching, Chao (Kaohsiung Medical University Chung-Ho Memorial Hospital, TW)
Nai-Fang, Chi (Taipei Veterans General Hospital, TW)

Product Application:

LT3001 is a novel small molecule designed to have reperfusion, anti-inflammation, and free radical scavenging activities. Its superior safety and efficacy over tPA in treating acute ischemic stroke during extended treatment time window was demonstrated using multiple thromboembolic stroke models. LT3001 was safe and well tolerated in healthy volunteers in a completed Phase 1 study and currently evaluated for safety and potential efficacy in acute stroke patients in US and Taiwan (NCT04091945). It is a multicenter, double-blind, single-dose, randomized, and placebo-controlled prospective Phase IIa clinical study, designed to evaluate LT3001 versus placebo control in subjects with AIS within 24 hours of stroke onset.

MEDTRONIC NEUROVASCULAR



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Director Government Affairs & External Relations Medtronic Neurovascular & CSF Solutions

Project/Trial:

Devices for Acute Stroke Interventional-Coordinated Registry Network (DAISI CRN) collaboration initiative. Launched by the FDA in 2017 and is supported by numerous physician-led organizations, societies, and industry sponsors such as Medtronic.

Investigational Product:

Solitaire™ X Revascularization Device

Potential Significance of Product:

The Solitaire™ X Revascularization Device encompasses a continuum of innovation and differentiated design characteristics and enhancements, resulting in exceptional ease-of-use handling and outstanding clinical outcomes.

Study Status:

DAISI CRN was developed with a focus on acute ischemic stroke that allows the capture of real-world practice data of patients treated for LVO strokes. The establishment of the CRN is to collect data and evidence needed for clinical and regulatory decision-making, post-market device surveillance, expanded indications and future prospective trials for pre-market approvals can be accumulated

Principal Investigators:

The DAISI CRN is led by co-chairs, Adnan Siddiqi from the University of Buffalo, Sameer Ansari from Northwestern, and David Liebeskind from UCLA. FDA representation is led by Avena Russell and Carlos Peña.

Product Application:

Medtronic's Solitaire™ X Revascularization Device is approved for use around the world and Medtronic is a partner of the DASISI CRN initiative. Medtronic Neurovascular is collaborating with physicians on continuing to build additional evidence in treating ischemic stroke, and that technology innovation continues to ensure better outcomes for patients.

MICROVENTION



STAIR XI Attendees:

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Company Statement:

Microvention is actively engaged in a number of research and development activities aimed at expanding and improving stroke treatment options.

**STAIR XI Attendees:**

Sylvain Durrleman, Head of Clinical and Medical Affairs: sylvain.durrleman@gmail.com
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Project/Trial:

A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Efficacy and Safety Study of MLC1501 in Patients with Stroke

Investigational Product:

MLC1501

Potential Significance of Product:

Beyond the acute phase, there are no available treatments, other than rehabilitation measures to relieve the disabilities suffered by stroke survivors.

Study Status:

Phase IIB/III under initiation, expected completion date 2024.

Sites/Locations:

47 sites in USA, Australia, Singapore, Taiwan, Korea

Principal Company Contacts:

Mr. David Picard, CEO: david.picard@moleac.com
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Product Application:

MLC1501 is being developed as a new treatment to improve functional independence and recovery of motor, speech, cognition and other neurological dysfunctions resulting from a stroke. MLC1501 is a botanical product, combination of only four herbal components – *Radix Angelicae sinensis*, *Rhizoma Chuanxiong*, *Radix Astragali* and *Radix Polygalae*.

MLC1501 is a simplified formulation of a parent compound marketed for more than twenty years in several Asian countries and who have demonstrated neuroprotective, anti-inflammatory and neurorestorative properties in nonclinical animal and cellular models of focal and global cerebral ischemia and traumatic brain injury (TBI). Systematic review of these clinical trials (including a double-blind RCT of more than 1100 patients, the CHIMES study) have demonstrated benefit in improving functional and neurological recovery, particularly in patients with post-acute ischemic stroke.

An IND for the development of MLC1501 as treatment for post stroke recovery has been granted in 2018 by the US FDA Neurology Division, and clinical development has started. An international global phase IIB/III study is currently being initiated including clinical centers in the US and 7 other countries.

**STAIR XI Attendees:**

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Project/Trial:

The PROVEN Trial, (Phase II to Restore Oxygen in Large Vessel Occlusion patients En Route for MT using NanoO₂TM)

Investigational Product:

NanoO₂ (Dodecafluoropentane emulsion, DDFPe)

Study Status:

Phase Ib/IIa complete, Phase II upcoming

Sites/Locations:

3 hub hospitals, several spoke hospitals. The hub hospitals are:

- Stanford University Medical Center
- University of Arkansas for Medical Sciences
- Washington Regional Medical Center

Principal Investigators:

Maarten Lansberg, MD, PhD, Professor of Neurology, Stanford University Medical Center,
Krishna Nalleballe, MD, Neurologist, University of Arkansas for Medical Sciences

Product Application:

NanoO₂ is a first-in-class drug for oxygen delivery being tested as a neuroprotectant for acute ischemic stroke. The drug's unique mechanism of action reduces resistance to oxygen transfer out of the bloodstream, and allows the blood flowing through the hypoperfused penumbra to offload a higher percentage of its oxygen. Increased oxygen delivery helps the penumbral tissue avoid inefficient anaerobic metabolism, energy failure, and death.

Additional Comments:**TARGETING A PROCESS NEAR THE TOP OF THE CHAIN OF EVENTS**

NanoO₂ targets a process near the top of the chain of events – hypoxia – and hits the target quickly and effectively. Pre-clinical studies consistently demonstrated over an 80% reduction in infarct volume.¹⁻⁵ A Phase Ib/II clinical trial demonstrated safety at all dose levels tested, and the high dose cohort had significantly better mRS at 30 days and 90 days than placebo (p=0.01, p=0.03).⁶ A Phase II clinical trial has been carefully designed to maximize patient benefit.⁷

EFFICIENT TRIAL DESIGN

The study will test the drug that has the strongest pre-clinical signal out of over 70 products later brought into trials, NanoO₂.⁸ The trial will test the patients in the greatest need – those with severe large vessel occlusions (LVOs).⁹ Patients will be enrolled at spoke hospitals after imaging confirms the presence of LVO and salvageable tissue.¹⁰ Patients will be treated with the standard of care along with either NanoO₂ or placebo.¹¹ NanoO₂ will be provided to increase oxygen delivery to maintain

penumbral tissue during the hours when the patient is being transferred to a hub hospital to undergo mechanical thrombectomy. Successful reperfusion should turn the preserved penumbral tissue into normally perfused tissue that can support long term functional independence.

HOW IT WORKS

NanO₂ is theorized to work with a unique mechanism of action that is different from any other substance tested in humans. The active pharmaceutical ingredient is a perfluorocarbon – a carbon chain surrounded by fluorine – an inert molecule that dissolves gasses like oxygen extremely well. In high oxygen environments, oxygen dissolves into the drug.¹² In low oxygen environments, oxygen diffuses out of the drug.¹³ The drug is made into nano-sized emulsion droplets that are injected intravenously.

Unlike other perfluorocarbon emulsions that have been tested in humans, pharmacokinetic studies show that after NanO₂ is injected intravenously, most of the drug quickly passes out of the bloodstream.^{14,15} In doing so, the drug is theorized reduce the resistance to the flow of oxygen out of the bloodstream.¹⁶

In the area distal to an occlusion, blood flow is reduced, but not to zero because collateral blood vessels still provide some blood flow.¹⁷ However, the blood flowing through hypoperfused tissue does not deliver most of its oxygen. A recent study showed that the oxygen extraction fraction of blood flowing through the most hypoperfused and hypoxic regions of the brain is less than 40% - meaning that 60% of the blood that flows into the tissue remains inside the red blood cells without being delivered.¹⁸ Because red blood cells are naturally tuned to be highly sensitive to changes in oxygen levels seen in hypoxic tissues, a drug that can cause small reductions in the resistance to oxygen flow can lead to dramatic increases in the amount of oxygen that red blood cells offload.¹⁹

WHAT WE HOPE TO SEE IN PHASE II

We hope to see an improvement in NIHSS even before reperfusion occurs.

NanO₂ is expected to increase oxygen delivery to the penumbra, allowing the tissue to avoid inefficient anaerobic metabolism and instead use aerobic metabolism which creates ~16x more energy per unit glucose. If energy production is high enough, the neurons should be able to start firing again.²⁰ Neuronal firing would be expected to be seen in immediate improvements on NIHSS. In fact, in animal studies using animal analogs to the NIHSS, animals given the drug see dramatic improvements within an hour despite having permanent occlusions.^{3,5} The NIHSS will be taken as part of the standard of care prior to the drug, again when the patient arrives at the hub hospital, and at several points after mechanical thrombectomy.

We hope to stop infarct growth.

Infarct volume will be estimated with imaging at several timepoints along with part of the standard of care. We hope that the drug will prevent infarct growth from the time period beginning as soon as the drug is administered, leading to a lack of growth by the time the patient arrives at the hub hospital. In animals, the drug has been shown to effectively stop infarct growth even up to 24 hours after stroke onset.²

We hope to increase the proportion of patients that will be eligible for thrombectomy upon arrival to the hub.

Some patients who meet the eligibility requirements for thrombectomy at the spoke hospital are no longer eligible by the time they get to the hub hospital because their infarcts have grown too large.²¹ We hope to see a reduction in the amount of patients who are ineligible for thrombectomy upon arrival to the hub due to infarct growth.

We hope to improve functional independence at 30 days and 90 days.

By keeping the penumbra alive in the short term until reperfusion can allow to live in the long term, we hope to see improvements in functional independence. While the prior Phase Ib/II saw significant improvements in the high dose cohort vs placebo, further trials are needed to repeat and validate the effect.⁶

References:

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OMNIOX



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Company Statement:

Omniox is actively engaged in a number of research and development activities aimed at expanding and improving stroke treatment options.

PENUMBRA, INC.



STAIR XI Attendees:

Tatiana Ermakova, MD, MPH: termakova@penumbranic.com

Project/Trial:

MIND: Artemis in Removal of Intracranial Hemorrhage

Investigational Product:

Artemis Neuro Evacuation Device

Study Status:

Enrolling

Sites/Locations:

USA, Canada, Germany

Principal Investigators:

Adam Arthur, MD

Product Application:

The primary objective of this multicenter randomized controlled study is to compare the safety and efficacy of minimally invasive hematoma evacuation with the Artemis Neuro Evacuation Device to best medical management for the treatment of intracerebral hemorrhage (ICH).

Additional Comments:

Subjects will be randomized to either minimally invasive hematoma evacuation with the Artemis Neuro Evacuation Device with medical management (MIS group) or best medical management alone (2:1) (MM).

PERFUZE



STAIR XI Attendees:

Wayne Allen, CEO

Project/Trial:

Millipede Clot Ingestion System (CIS)

Investigational Product:

Millipede Clot Ingestion System (CIS)

Potential Significance of Product:

Our vision, for patients treated with thrombectomy, is to increase the number of stroke survivors that can live functionally independent lives.

Product Application:

Our unique catheter technology platform is designed to achieve superior clinical outcomes in shorter procedural times; resulting in fast, safe, cost-effective clot extraction from the brain. In August 2019, Perfuze received a Breakthrough Device Designation Status from the FDA for its Millipede CIS (Clot Ingestion System).

PRA HEALTH SCIENCES



STAIR XI Attendees:

Bill Holt: holtbill@prahs.com

Project/Trial:

PRA Health Sciences is a top global CRO company. PRA has assisted in conducting multiple clinical trials in the stroke arena. Through this collaborative research, PRA has helped to develop life-saving and life-improving drugs and devices in the acute treatment of stroke.

PRA invites new opportunities to partner with organizations and investigators to rapidly launch and complete important new stroke research studies by optimizing our comprehensive clinical development services including data capture and management, statistical analysis, clinical trial management, medical writing, and regulatory and drug development consulting.

PROLONG PHARMACEUTICALS



STAIR XI Attendees:

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Ron Jubin, Innovation: rjubin@prolongpharma.com

Project/Trial:

Pp-007: A Clinical Stage Investigational Product in development for Treatment of Acute Ischemic Stroke

Investigational Product:

Pp-007 (PEGylated carboxyhemoglobin, bovine)

Potential Significant of Product:

The unique biological properties of Pp-007 (PEGylated carboxyhemoglobin, bovine) are anticipated to provide significant clinical benefits in AIS beyond current standard of care. Early and rapid administration of PP-007 in conjunction to thrombolysis or thrombectomy could significantly improve cerebral blood flow to the infarcted region. After initial delivery of CO, PP-007 may promote the delivery of O₂ to the penumbra that is potentially helpful to reduce local inflammation and tissue hypoxia. Collectively these properties have the potential to reduce infarct volumes and improve neurological deficits. The clinical development program for PP-007 is designed to evaluate the safety and efficacy of PP-007 in AIS to provide added clinical benefits over current standard of care.

Study Status:

Phase 1

Investigator/Sites:

- **Italo Linfante MD, FAHA**, Baptist Health South Florida, Miami, FL
- Raul Gomes Nogueira, MD, Emory University Hospital, Grady Memorial Hospital, Atlanta, GA
- Ricardo Hanel, MD, PhD – PI, Baptist Health Research Institute, Jacksonville, FL
- Ruchir Shah, MD, Chattanooga Center for Neurologic Research, Chattanooga, TN
- Pascal Jabbour, MD, Thomas Jefferson University Hospitals, Cooper University Health Care, PA
- Wayne M. Clark, MD, Oregon Health & Science University, Portland, OR

Product Application:

PP-007: A Clinical Stage Investigational Product in Development for Treatment of Acute Ischemic Stroke with multiple biological properties to treat the complex pathophysiology of stroke.

PP-007 (PEGylated carboxyhemoglobin, bovine; SANGUINATE) is a unique intravenous, gas transfer agent being developed for the treatment of hypoxic disorders including acute ischemic stroke. Its components include the oxygen carrying component bovine hemoglobin (O₂), Polyethylene glycol (PEG) and Carbon monoxide (CO). The components function together to provide unique biological benefits. Various *in vitro* and *in vivo* studies have indicated that PP-007 can readily act within regions of vascular blockage and associated tissue hypoxia. These experiments have shown PP-007 can improve blood flow rheology through reduced vascular vasoconstriction. The gas transfer properties include the initial release of CO that has been associated with reduction in inflammation and lastly, the targeted delivery of O₂ to regions of severe hypoxia. PP-007 has been evaluated in several animal models including the transient middle cerebral artery occlusion (tMCAO) rat models. A separate study was conducted in a permanent

middle cerebral artery occlusion (pMCAO) canine stroke model to expand upon the rodent studies in a large animal model. Outcomes were similar wherein the dogs that received PP-007 treatment exhibited improved collateral circulation and reduced infarct volumes. These data confirmed the findings of the rodent models and further suggested a treatment potential of PP-007 in AIS that cannot be treated by thrombectomy or thrombolytic therapy. These data collectively indicated that PP-007 drug product contributed to reduced brain damage across all studies while showing other improvements (i.e., collateral flow, tissue oxygenation, reduction of inflammation) where measured. The improvement in neurological scores further indicated outcome effects were also associated with functional improvements. Lastly, the ability of the product to improve some outcome measures close/concurrently/following reperfusion indicated PP-007 may have a broader treatment window than anticipated with single action agents. Clinical trials of PP-007 in patients with acute ischemic stroke are planned for initiation.

Additional Comments:

Phase 1 Study initiation planned 4Q2020



STAIR XI Attendees:

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Summary:

RapidAI –

- is currently involved with numerous clinical trials, including several industry sponsored trials that use RAPID to select eligible patients.
- is the sponsor for several studies evaluating new RAPID software products. (Below is an overview of current ongoing studies sponsored by RapidAI or industry partners.)
- supports more than 20 investigator-initiated studies

Clinical Trials:

APRIL

Objective: To evaluate if ApTOLL is safe, well tolerated and shows any biological effect in AIS patients due to LVO

Status: Enrolling

PI: Dr. Carlos Molina Cateriano (University Hospital of Vall d'Hebron)

Sponsor: AptaTarget

Countries: 3

ANGEL

Objective: To establish the efficacy of EVT in patients with AIS from LVO in the anterior circulation and having a moderate-large pre-treatment infarct volume.

Status: Enrolling

PI: Dr. Zhongrong Miao (Tiantan Hospital)

Countries: 1

CHARM

Objective: Evaluate the efficacy and safety of i.v. BIIB093 for severe cerebral edema following large hemispheric infarction

Status: Enrolling

Sponsor: Biogen

Countries: 7

ENCHANTED2

Objective: To establish the effects of intensive BP lowering in AIS patients with successful recanalization after MT

Status: Enrolling

PI: Dr. Jian Min Liu, Dr. Pengfei Yang (Changhai Hospital), Dr. Craig Anderson (TGI)

Sponsor: TGI

Countries: 1

ImPACT-P

Objective: Assess the efficacy of augmenting CBF to preserve the penumbra in AIS patients

Status: Enrolling

PI: Dr. Yoram Solberg (Brainsgate)

Sponsor: Brainsgate

Countries: 1

SELECT 2

Objective: Evaluate the safety and efficacy of endovascular thrombectomy in AIS patients with a large core

Status: Enrolling

PI: Dr. Amrou Sarraj (UTH)

Countries: 5

TIMELESS

Objective: Evaluate the efficacy and safety of Tenecteplase compared with placebo in patients with AIS and evidence of salvageable tissue on their baseline imaging

Status: Enrolling

PI: Dr. Gregory Albers (Stanford University)

Sponsor: Genentech

Countries: 2

RapidAI Sponsored Studies:

- Rapid for Angio
- Rapid Aneurysm
- SurgicalPreview®
- Rapid LVO 2.0
- Rapid ICH 2.0
- Rapid ASPECTS 2.0

Investigator-Initiated Studies:

General Topics:

- Posterior Circulation
- Gender and AIS
- Hyperoxia
- Clinical Workflow
- Hemorrhage
- Large Core
- Golden Hour

SHIN POONG PHARM



STAIR XI Attendees:

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Jei-Man Ryu, Ph.D, RPh – President; jeimryu@shinpoong.co.kr

Project/Trial:

A prospective, randomized, double-blind phase IIb clinical trial to investigate the efficacy and safety of SP-8203 in patients with acute ischemic stroke requiring rtPA standard of care (NCT04479449).

Investigational Product:

Otaplimastat (code: SP-8203)

Study Status:

- 1) Study Phase: Phase IIb
- 2) Number of Subjects: 178 subjects
- 3) Study Status: Recruiting (Currently, 99% of enrollment has been completed, expecting completion of patient enrollment by early September.)

Sites/Locations:

The study is being conducted at 13 clinical sites in South Korea: 31) Asan Medical Center
2) Kyunghee University Medical Center
3) Korea University Guro Hospital
4) Myongji Hospital
5) Soonchunhyang University Hospital
6) Pusan National University Hospital
7) Inje University Hospital
8) Seoul National University Bundang Hospital
9) Ulsan University Hospital
10) Dong-A University Hospital
11) Chonnam National University Hospital
12) Nowon Eulji Medical Center
13) Kyungpook National University Hospital

Principal Investigators:

No.	Name (Neurologist)	CI & PI	Institutions
1	Jong S. Kim, MD, PhD	Study Coordinating Investigator	Asan Medical Center
2	Dae-il Chang, MD, PhD	Study Principal Investigator	Kyunghee University Medical Center
3	Kyungmi Oh, MD, PhD	Study Principal Investigator	Korea University Guro Hospital
4	Jong-Ho Park, MD, PhD	Study Principal Investigator	Myongji Hospital
5	Kyung Bok Lee, MD, PhD	Study Principal Investigator	Soonchunhyang University Hospital

6	Sang Min Sung, MD, PhD	Study Principal Investigator	Pusan National University Hospital
7	Eung-Gyu Kim, MD, PhD	Study Principal Investigator	Inje University Hospital
8	Hee-Joon Bae, MD, PhD	Study Principal Investigator	Seoul National University Bundang Hospital
9	Jee-Hyun Kwon, MD, PhD	Study Principal Investigator	Ulsan University Hospital
10	Jae Gwan Cha, MD, PhD	Study Principal Investigator	Dong-A University Hospital
11	Man Seok Park, MD, PhD	Study Principal Investigator	Chonnam National University Hospital
12	Jong Moo Park, MD, PhD	Study Principal Investigator	Nowon Eulji Medical Center
13	Yang Ha Hwang, MD, PhD	Study Principal Investigator	Kyungpook National University Hospital

Product Application:

Otaplimastat (a.k.a. SP-8203) is a quinazoline-2,4-dione derivative developed as a cytoprotectant with multi-target-directed anti-ischemic activities including metalloprotease pathway inhibition through specific binding to CD147 and an antioxidant enzyme, Mn-SOD induction. In addition to anti-ischemic efficacy as a monotherapy in animal stroke models, it also reduces rtPA-induced mortality, intracerebral hemorrhage (ICH), and edema even when reperfusion is delayed.

In a phase 2a study conducted as a randomized, double-blind, placebo-controlled, multicenter study in 80 stroke patients (19-80 years old) receiving tPA (within 4.5 hours after the onset), intravenous otaplimastat (administered <30 minutes after rtPA) was well-tolerated.¹ No symptomatic intracranial hemorrhage (sICH) and major systemic bleeding within 5 days were observed; there was no significant difference in mortality, and in incidence rates of adverse events (AEs), treatment-emergent AEs (TEAEs) and serious adverse events (SAEs) between placebo and treatment groups. The currently ongoing phase 2b study is similarly designed but expanded to 178 stroke patients, evaluating the efficacy and safety of the combination therapy of rtPA and otaplimastat (one dose; 40 mg/dose, 6 times with 12 h interval) in a randomized, double-blinded manner. The primary endpoint is the neurological improvement evaluated in NIHSS scores up to 28 days to re-confirm the favorable trend of quickly diminishing neurological deficits shown in Phase 2a study in a larger population. Although the small size precludes any firm conclusion, the post-hoc analyses of Phase 2a study suggested that it is unlikely that otaplimastat reduces ICH or improves recanalization. Rather, the favorable trends of clinical outcomes are accompanied with reduction in MRI-identified infarct volumes, possible in line with pleiotropic neuroprotective mechanisms preclinically elucidated. Thus, in the Phase 2b study, the clinical outcomes (NIHSS changes and 90-day mRS distribution) will be evaluated in correlation with TICI scores (indicators for the degree of recanalization) and ICH volumes. Currently, 176 of 178 target patients are enrolled for Phase 2b study. The overall occurrence of baseline characteristics and safety outcomes of all enrolled patients seems to be comparable with those of phase 2a study with slight difference. Briefly, there have been no adverse drug reaction (ADR) related to investigational product in overall. The incidence rate of SAEs and mortality rate are 17.1% and 5.1%, respectively. The incidence rate of sICH was reported as 3.4% based on ECASS II criteria.^{2,3}

¹Safety and Efficacy of Otaplimastat in Patients with Acute Ischemic Stroke requiring tPA (SAFE-TPA): A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Study., Jon S. Kim *et al.*, ANN NEUROL 2020;87:233-245

²Symptomatic Intracranial Hemorrhage following Intravenous Thrombolysis for Acute Ischemic Stroke: A critical Review of Case Definitions. Raymond C.S. Seet *et al.*, Cerebrovasc Dis 2012; 34: 106–114.

³Hemorrhagic Transformation of Ischemic Brain Tissue: Asymptomatic or Symptomatic? Christian Berger *et al.*, Stroke 2001; 32: 1330–1335

SIMCERE



STAIR XI Attendees:

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Project/Trial:

Effect of Edaravone and Dexborneol Concentrated Solution for Injection on Treatment of Acute Ischemic Stroke (AIS)

Investigational Product:

Edaravone and Dexborneol Concentrated Solution for Injection (EDC)

Potential Product Significance:

EDC is an effective and safe therapy, superior than Edaravone alone. This provided a novel, better treatment option for patients with AIS.

Study Status:

NDA approval in China on Jul. 29th, 2020

Principal Investigators:

Dr. Wang Yongjun, Beijing Tiantan Hospital, Capital Medical University

Product Application:

Treatment for acute ischemic stroke

Additional Comments:

A randomized, double-blind, positive controlled (Edaravone), Phase 3 clinical trial was conducted in 1200 patients to evaluate the efficacy and safety of EDC for treatment of AIS. And the outcome showed: EDC is statistically superior than Edaravone alone (EDV) for the primary efficacy endpoint (mRS at day-90).

STRYKER NEUROVASCULAR



STAIR XI Attendees:

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Project/Trial:

Stryker Neurovascular is actively engaged in a number of research and development activities aimed at expanding and improving stroke treatment options.

SYNTHEON



STAIR XI Attendees:

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President Syntheon LLC

Project/Trial:

RapidPulse

Investigational Product:

RapidPulse Aspiration System

Study Status:

Pre-Clinical

Principal Investigators:

Dr. Raul Nogueira

Product Application:

Next Generation Aspiration System



STAIR XI Attendees:

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Company Statement:

VIZ.ai is actively engaged in a number of research and development activities aimed at expanding and improving stroke treatment options.



STAIR XI Attendees:

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Project/Trial:

- RHAPSODY (Phase II)
- RHAPSODY-2 (Phase III)

Investigational Product:

3K3A-APC

Potential Significance of Product:

3K3A-APC, a mutant variant of Activated Protein C (APC), is a novel, multiple-target, multiple-action neurovascular therapy that impacts several steps in the ischemic cascade resulting in brain protection after ischemic stroke. 3K3A-APC has been shown to protect the entire neurovascular unit—endothelial, glial, and neuronal cells—utilizing multiple, novel protective mechanisms that have been identified at the level of membrane receptors and intracellular signaling pathways. Considerable pre-clinical data suggest 3K3A-APC effectively reduces infarct volume, ameliorates behavioral deficits, and reduces or eliminates tissue plasminogen activator (tPA)-related hemorrhage after focal ischemia in a variety of experimental stroke models. Data from a Phase 2 study in patients with ischemic stroke indicate that treatment with 3K3A-APC might reduce post-tPA and/or thrombectomy intracranial bleeding that is associated with poor outcome in patients with ischemic stroke.

There is a lack of approved effective treatments for ischemic stroke. The current standard of care (SOC) includes use of t-PA thrombolysis or mechanical thrombectomy, or both; these treatments carry significant risk of post-treatment intracranial bleeding and are consequently inconsistently used by treating physicians despite considerable evidence supporting their beneficial potential. Fear of hemorrhagic complications inhibits many physicians from using thrombolysis or thrombectomy; successful development of 3K3A-APC to reduce post-reperfusion hemorrhage could significantly benefit patient by promoting wider use of thrombolysis and thrombectomy by hesitant physicians.

Study Status:

Phase 2 completed. Planning Phase III now.

Principal Investigators:

Patrick D. Lyden, MD, FAAN, FANA, FAHA, FESO
Professor of Physiology and Neuroscience
Professor of Neurology
Zilkha Neurogenetics Institute
Keck School of Medicine
University of Southern California

Product Application:

The US Food and Drug Administration (FDA) has designated the investigation of the company's experimental drug 3K3A-APC for the treatment of acute ischemic stroke as a Fast Track development program.

Additional Comments:

RHAPSODY was conducted in NeuroNEXT under a grant from NINDS. RHAPSODY-2 is the subject of a grant submitted to NINDS to conduct the study in StrokeNet.