From: John Redaelli <jjrinhb@aol.com>
Date: Thursday, August 24, 2023 at 12:58 PM
To: Lana Moralez <lmoralez@cirm.ca.gov>
Subject: [EXT] Fw: From: John Redaelli Re: My 2nd "Public Comment" - August 25 Task Force on Neuroscience and Medicine Meeting

From: John Redaelli (California Resident)

To: Lana Moralez (CIRM) lmoralez@cirm.ca.gov

Re: My 2nd "Public Comment" - August 25 Task Force on Neuroscience and Medicine Meeting

Date: Thursday, August 24, 2023

Hello Lana...

John Redaelli, here again...I don't mean to test your patience, and I greatly appreciate your generosity...

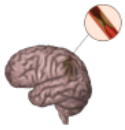
If it's not too much trouble I hope you might consider allowing me to add a **2nd Public Comment**, to pass along to the **August 25 Task Force on Neuroscience and Medicine Meeting**...

Athersys, today - Thur., Aug, 24, 2023, UPDATED their Corporate Presentation (pdf):
s23.q4cdn.com/674737627/files/doc_presentations/2023/Athersys-Corporate-Summary.pdf

Slides #12 - 17, As it relates to Ischemic Stroke -

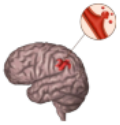
Stroke Overview

Background



Ischemic Stroke

Caused by a blocked artery



Hemorrhagic Stroke

Caused by leaking or bursting of a blood vessel

- A stroke occurs when the blood supply is interrupted or reduced to part of the brain. This prevents brain cells from getting oxygen and nutrients, leading to cell death and tissue loss
- Stroke is the **leading cause of disability** and the **third leading cause of death** in the US
- Each year nearly **800,000** people in the US suffer a stroke
- About **43%** of all strokes are **moderate to severe ischemic strokes**, the focus of our trial

Impact

High Unmet Need
Only 30% of patients qualify for current standard of care (thrombolytics / mechanical thrombectomy) both of which have limited treatment windows and patient eligibility

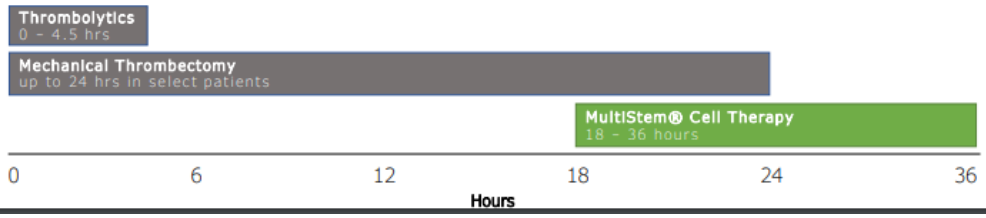
High Burden on Healthcare System
Stroke patients have a $55 billion impact on the healthcare system

MultiStem Solution
-Expands treatment window to 36 hours
-Potential to provide additive benefit to standard of care
-Treats bodily response to clot formation and prevents secondary injury and complications caused by the stroke

Unmet Medical Need in Stroke: Only 2 Approved Ischemic Stroke Treatments

	Thrombolytics	Mechanical Thrombectomy	MultiStem® Cell Therapy
Mechanism of Action	Clot dissolving medications	Removal of the clot using a catheter device	Modulation of the immune system
Applicability	**Only 15%** of ischemic stroke patients are eligible for tPA within 4.5 hours	**Only ~10%** of ischemic stroke patients are eligible due to the location of the clot	Potentially applicable to **90 - 95%** of all ischemic stroke patients because of extended therapeutic window and mechanism of action
Benefit	Improved recovery in ~15% of patients who receive tPA at 90 days **with little additional improvement at Day 365**	Improved recovery comparable to tPA at 90 Days with **no clinically meaningful improvement from 90-365 Days**	Promotes recovery, projected clinically meaningful benefit. Can be given independently or following thrombolytics and/or thrombectomy **at both 90 Days and 365 Days**
Safety / Complications	Associated with hemorrhagic transformations in 2 - 4% of patients	Potential vascular damage and cerebral edema	2 completed studies and 3rd ongoing with a **favorable tolerability profile**

Therapeutic Window



Clinical Trials
MultiStem for Ischemic Stroke

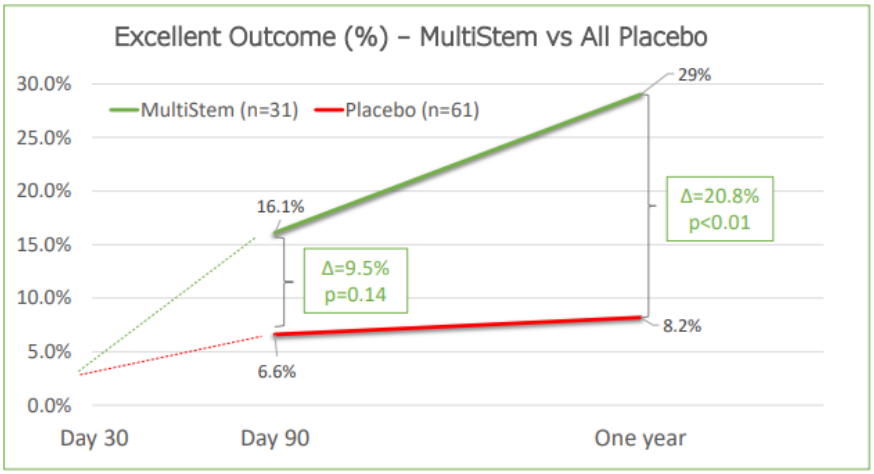
	MASTERS-1	TREASURE (Heallos)	MASTERS-2
Phase - # Subjects	Phase 2 - 126 subjects	Phase 2/3 - 206 subjects	Phase 3 - 300 subjects
Date Conducted	2010 - 2016	2017 - 2022	2018 - Present
# Sites - Countries	33 - US, UK	48 - Japan	39 - US, UK, EU, Taiwan, Australia
Endpoints	**Primary** - Global stroke recovery at day 90	**Primary** - Excellent Outcome at day 90	**Primary** - mRS shift at 365 days

Results	• Primary Endpoint missed
	• Subset of patients who received MultiStem within 36 hours saw improvement in:
	  • Excellent Outcome, Δ=20.8%, p<0.01 at day 365
	  • mRS shift analysis, p=0.07 at day 365
		• Primary Endpoint missed
		• Patients who received MultiStem saw improvement in:
		  • Global Recovery at day 365: Δ=12.2%, p<0.05
		  • Barthel Index ≥95 at day 365: Δ=13.1%, p=0.05
			• Interim analysis expected to take place Q4 2023
			• Full enrollment expected Q2 2024
			• Data readout expected Q2 2025

Key Takeaways	• Identified optimal time of administration (24-36 hours)	• Confirmed optimal time of administration • Confirmed that cells convey long term meaningful benefit beyond 90 days • Observation that Excellent Outcome is a challenging primary outcome in aged population	• Ongoing

MASTERS-1: Phase 2 Ischemic Stroke Trial Results
Treatment with MultiStem Shows Meaningful Benefit

Proportion of Subjects Treated within 36 Hours Achieving Excellent Outcome Increases Over Time
(Excellent Outcome = Patients Achieving NIHSS 0 or 1 and mRS 0 or 1, and Barthel Index ≥95)



Safety: Intravenous MultiStem well-tolerated by stroke patients, with no serious adverse reactions

Validation: Based on MASTERS-1 data, the stroke program was granted Fast Track and RMAT designation from the FDA

TREASURE Study by HEALIOS KK in Japan

Topline Data Announced May 2022 and Full Data in October 2022

- ✓ Sakigake designation
- ✓ 206 patients with moderate-to-moderate-severe strokes
- ✓ 48 trial sites in Japan
- ✓ Single cell therapy dose (1.2B cells) delivered intravenously within 18-36 hours following stroke onset or last known normal
- ✓ **Informed KOL panel and FDA Type B meeting to ensure that full potential benefit of MultiStem therapy is captured in our Phase 3 trial**

Favorable results at one year in recovery measures

- Indicates achievement of functional independence
- Reflects clinically relevant recovery in MultiStem® treated patients compared to placebo patients

One Year	MultiStem	Placebo	p-value*
Excellent Outcome	15.4%	10.8%	n.s.
Global Recovery	27.9%	15.7%	p<0.05
Barthel Index >=95	35.6%	22.5%	p=0.05

Excellent Outcome = mRS<=1, NIHSS<=1 and Barthel Index>=95
Global Recovery = mRS<=2, NIHSS Δ >=75% and Barthel Index>=95
* Prespecified covariance adjustment based on stratification factors

Ischemic Stroke (MASTERS-2)

Ongoing Pivotal Phase 3 Study

Randomized, double-blind, placebo-controlled clinical trial, actively enrolling up to **300 patients in leading stroke centers** in U.S. and internationally, under SPA agreement

IV administration of 1.2 billion MultiStem® cells or placebo; based on successful results from Phase 2, treatment window moved earlier to **18 - 36 hours** after stroke onset

New Perspective – TREASURE data offered a unique opportunity to reevaluate MASTERS-2 trial design by leveraging the collective data of MASTERS-1 and TREASURE

Successful FDA Type B meeting resulted in 4 modifications:

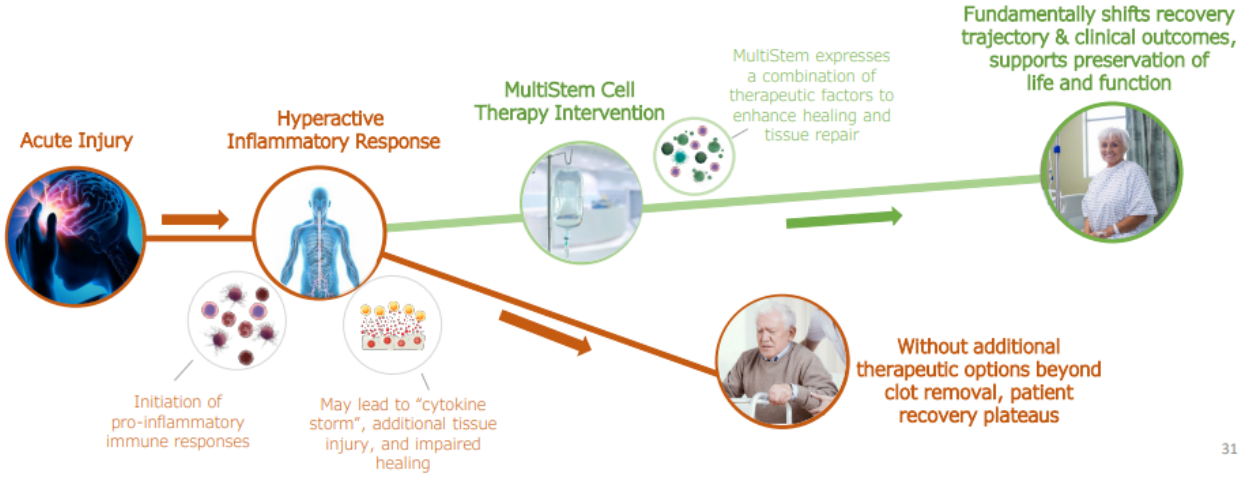
- Primary efficacy endpoint: Modified Rankin Scale **(mRS) Shift from day 90 to day 365**
- **Removed all eligibility caps** on concomitant reperfusion therapy (e.g., tPA, MR or tPA+MR) to reflect current standard of care
- Added option for **interim analysis** to assess sample size
- **Reordered several secondary endpoints** to prioritize Day 365

Interim analysis projected for October 2023
Full enrollment projected in 2Q 2024
Data read out projected in 2Q 2025

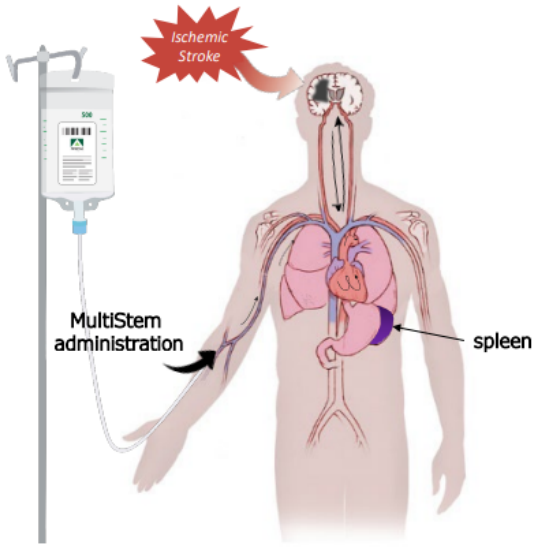
Slides #31 - #33, MultiStem Overview & Mechanism of Action (MOA) -

MultiStem® Overview

Our data show that **early intervention** with **MultiStem therapy** after an acute injury enhances healing by regulating an overactive immune response and re-establishing homeostasis.



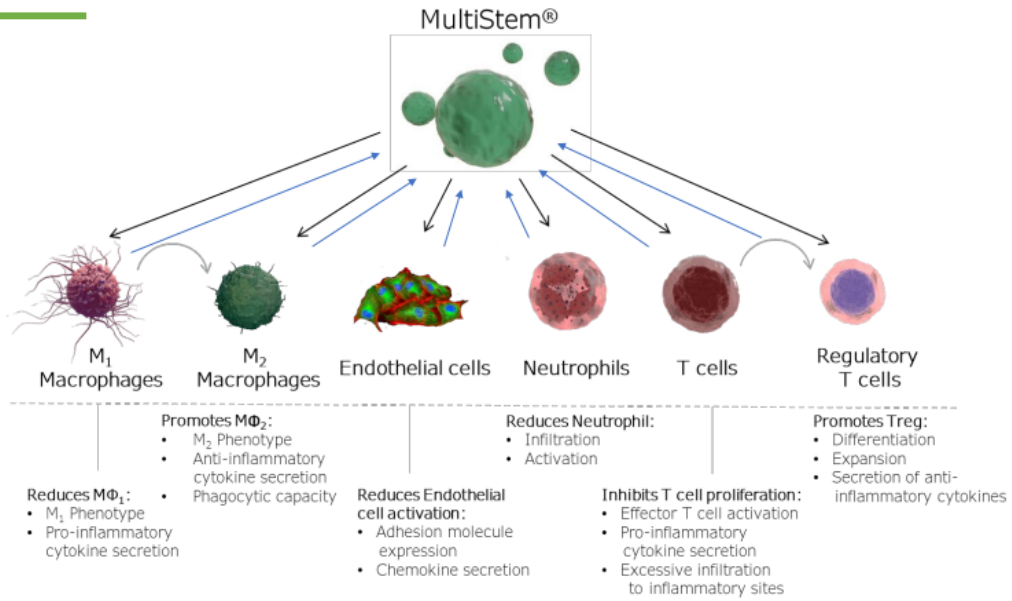
Key Events and Therapeutic Mechanism of Action of MultiStem following Ischemic Stroke



1. Ischemic stroke occurs when a blood clot blocks an artery leading to the brain, resulting in a corresponding loss of neurologic function.
2. Inflammation after stroke can lead to greater tissue loss and scarring in the brain and immune cells coming from the spleen play a major role this response.
3. MultiStem cells administered 18-36 hours post stroke migrate to the spleen, modulate splenic activation and peripheral immune responses.
4. The MultiStem-mediated decrease in pro-inflammatory signaling (ex, TNF, IL1β, IL-6) and increase in reparative immune responses (ex, T regulatory cells) results in a more favorable environment in the brain for long term repair and restoration of function.

Representative Publication in *Stem Cells (2017)*: MAPCs Enhance Recovery After Stroke by Modulating the Immune Response from the Spleen

Multimodal Mechanism of Action: A Living and Dynamic Product Capable of Interaction with Multiple Cell Types



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Slide #34, Biomarkers -

Consistent Biomarker Impact Observed in Preclinical and Clinical Studies Reflect Mechanism of Action

MultiStem subjects compared to Placebo subjects
Biomarker Levels at Day 7 relative to Baseline

Cytokine	MUST-ARDS 20 MS, 10 P	MASTERS-1 (Ischemic Stroke) 65 MS, 61 P
IL-6	↓	↓↓
IL-12	↓↓	↓
IL-1b	↓↓	↓↓
IFNg	↓↓	↓↓
TNFa	↓	↓↓

Reduction in acute inflammatory biomarkers from MultiStem treatment observed in ARDS and Ischemic Stroke patients, consistent with previously published preclinical data

Slides #36 & #37, Manufacturing -

Expansion Capabilities of MultiStem

- MultiStem is cell therapy based on MAPC® technology that can **double rapidly in culture** and have **robust expansion capabilities,** beyond other bone marrow-derived cell therapies, as seen in the chart to the left comparing MultiStem to MSCs
- **Hundreds of thousands of doses** can be generated from one single donor
- Cells are expandable in bioreactors with **~10x greater output** which enables us to **scale production** with **significant reduction in cost per dose**
- **Demonstrated product stability** – long shelf life for MultiStem product, >5 years
- Extensive characterization of the product including two proprietary **potency assays**

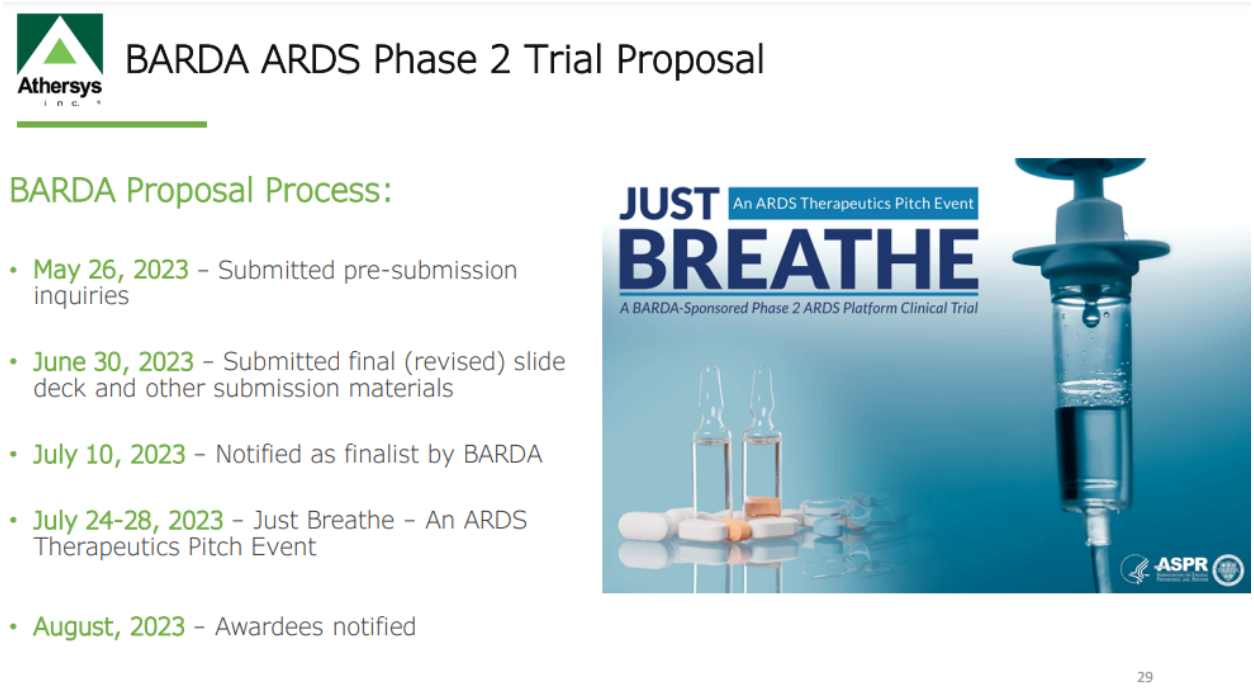
Scalable Manufacturing Process

15 Years of Production Experience and Advancements in Cell Therapy:

- Proven expertise in efficient, high yielding and innovative processes
- Establishment of an essentially closed manufacturing process - unique characteristic in the Cell & Gene Therapy industry
- Advancement of a large-scale cell therapy manufacturing process at increasing scales to support commercial manufacturing – building upon expertise from Cell Factories to Bioreactors

T-Flask	2D	3D 1.0	3D 2.0
• Used in Process Development Activities • Pre 2007	• 10 Layer Cell Factory • Year 2007 to present • ~ 6 Doses per Batch • 150 Production Runs Completed **Most Cell Therapy Companies are Here**	• 4 x 40 Liter Single Use Bioreactors • Year 2017 to 2020 • 20 – 25 Doses per Batch • 20+ Production Runs Completed	• 1 x 200L FPI/1 x 500L DP Single Use BRs • 2020 to present • 75-100 Doses per 500 L Bioreactor • 2 Development Runs Completed • Xeno-free process

Slide #29, Selected as finalist for the Biomedical Advanced Research and Development Authority's (BARDA) ARDS Therapeutics Pitch Event, Just Breathe -



Lana, again, I kindly ask that you might consider (As you did with my 1st Public Comment) forwarding all this to the members of the Neuro Task Force...

I Can't Thank You Enough!...

Best Wishes...

John Redaelli
e-mail: jjrinhb@aol.com