LONGEVERON

Cell-Based Therapies



A Regenerative Medicine Company

August 2023

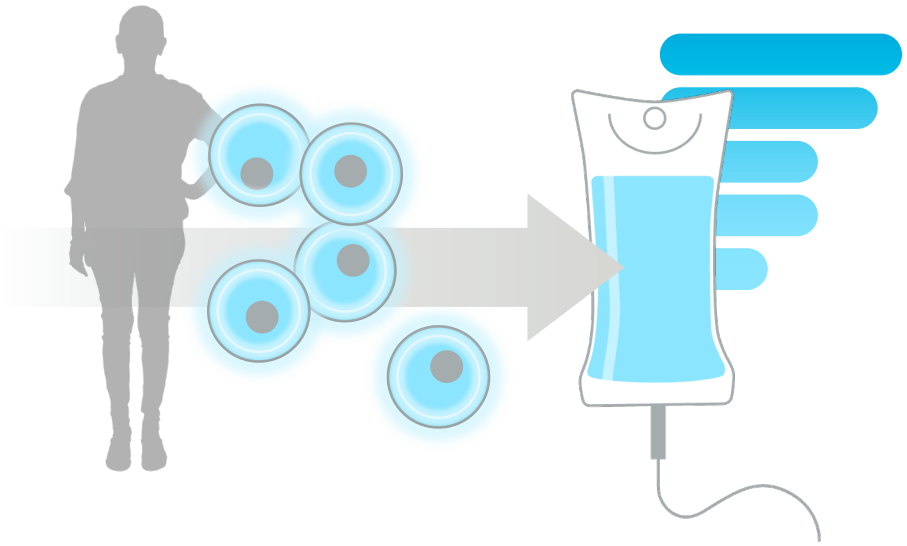
Forward Looking Statements

Certain statements in this presentation that are not historical facts are forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, which reflect management's current expectations, assumptions, and estimates of future operations, performance and economic conditions, and involve risks and uncertainties that could cause actual results to differ materially from those anticipated by the statements made herein. Forward-looking statements are generally identifiable by the use of forward-looking terminology such as "believe," "expects," "may," "looks to," "will," "should," "plan," "intend," "on condition," "target," "see," "potential," "estimates," "preliminary," or "anticipates" or the negative thereof or comparable terminology, or by discussion of strategy or goals or other future events, circumstances, or effects. Factors that could cause actual results to differ materially from those expressed or implied in any forward-looking statements in this release include, but are not limited to, statements regarding the offer and sale of securities, the terms of the offering, about the ability of Longeveron's clinical trials to demonstrate safety and efficacy of the Company's product candidates, and other positive results; the timing and focus of the Company's ongoing and future preclinical studies and clinical trials and the reporting of data from those studies and trials; the size of the market opportunity for the Company's product candidates, including its estimates of the number of patients who suffer from the diseases being targeted; the success of competing therapies that are or may become available; the beneficial characteristics, safety, efficacy and therapeutic effects of the Company's product candidates; the Company's ability to obtain and maintain regulatory approval of its product candidates in the U.S., Japan and other jurisdictions; the Company's plans relating to the further development of its product candidates, including additional disease states or indications it may pursue; the Company's plans and ability to obtain or protect intellectual property rights, including extensions of existing patent terms where available and its ability to avoid infringing the intellectual property rights of others; the need to hire additional personnel and the Company's ability to attract and retain such personnel; the Company's estimates regarding expenses, future revenue, capital requirements and needs for additional financing; the Company's need to raise additional capital, and the difficulties it may face in obtaining access to capital, and the dilutive impact it may have on its investors; the Company's financial performance and ability to continue as a going concern, and the period over which it estimates its existing cash and cash equivalents will be sufficient to fund its future operating expenses and capital expenditure requirements. Additionally, Longeveron makes no assurance that any public offering of its securities as described herein will occur at all, or that any such transaction will occur on the timelines, in the manner or on the terms anticipated due to numerous factors. Further information relating to factors that may impact the Company's results and forward-looking statements are disclosed in the Company's filings with the Securities and Exchange Commission, including Longeveron's Annual Report on Form 10-K for the year ended December 31, 2022, filed with the Securities and Exchange Commission on March 14, 2023 and its Quarterly Report on Form 10-Q for the second quarter of 2023 filed with the SEC on August 11, 2023. The forward-looking statements contained in this presentation are made as of the date of this presentation, and the Company disclaims any intention or obligation, other than imposed by law, to update or revise any forward-looking statements, whether as a result of new information, future events, or otherwise.

Our Mission: Deliver Regenerative Medical Therapies for Unmet Medical Needs

Lomecel-B™ -- A Pipeline in a Product

Allogeneic medicinal signaling cells (MSCs) isolated from bone marrow of healthy young adults



Three Clinical-Stage Programs

- **Hypoplastic Left Heart Syndrome: (Open-label Ph. 1 data led to Rare Disease, Orphan Disease and Fast Track FDA Designations): Ongoing Phase 2 trial (ELPIS II)**
- **Aging-Related Frailty: Ongoing Phase 2 trial in Japan**
- **Alzheimer's Disease: Enrollment completed in Phase 2a trial**

Longeveron Overview

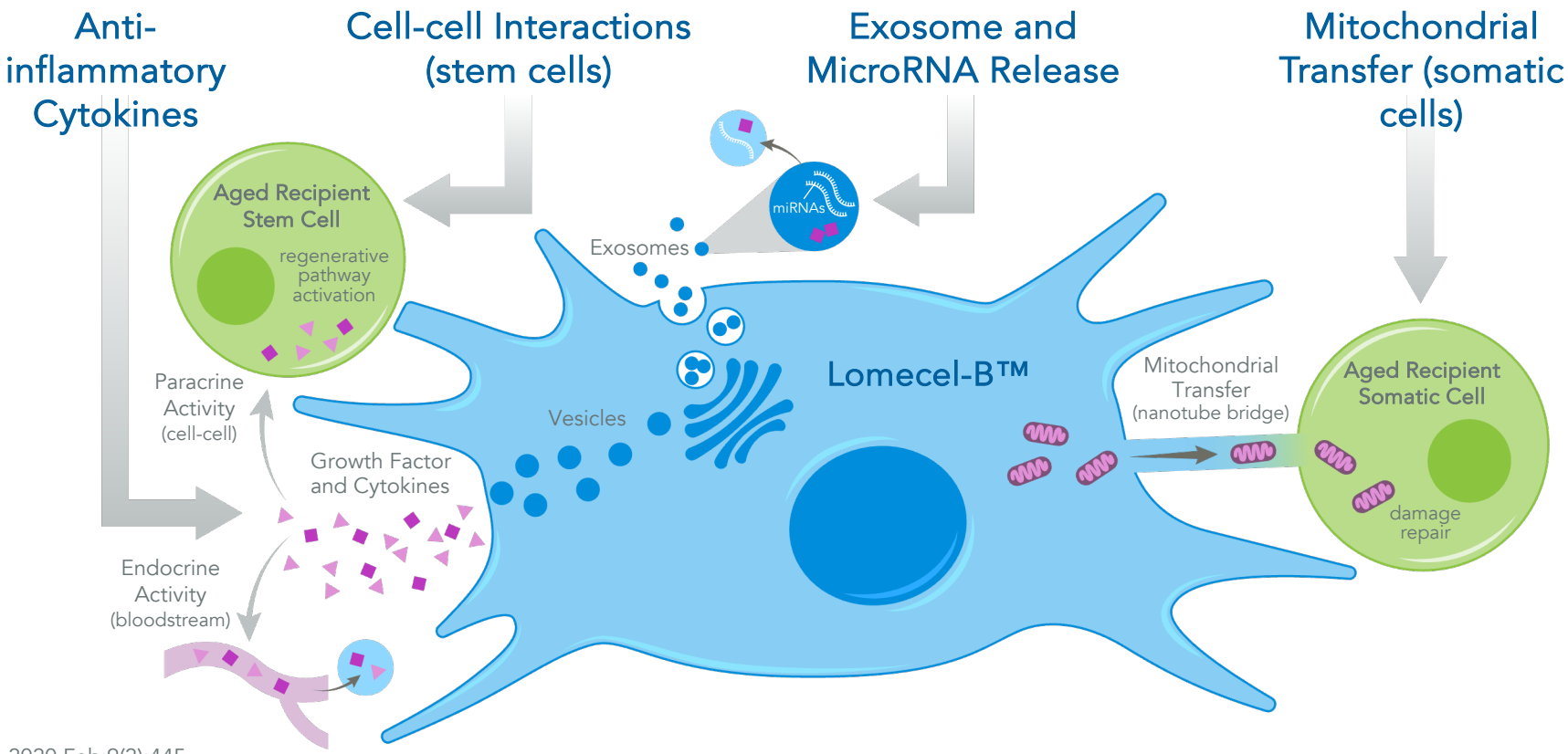
- Leader in development of MSCs for therapeutic indications
- Well-characterized allogeneic MSC (Lomecel-B™) product in Phase 2 trials
- Robust clinical pipeline with clinical efficacy signals in multiple indications with large unmet need: Alzheimer's Disease, Aging-Related Frailty, and HLHS
- Proven management, scientific, and manufacturing teams
- Solid balance sheet — cash into the 1st quarter of 2024
- On-site GMP facility for production of Lomecel-B™ (not dependent on CDMO)

Lomecel-B™ : Multiple Mechanisms of Action (MOA)

Pro-vascular, Pro-regenerative and Anti-inflammatory: Repairs Tissue and Promotes Healing

LOMECEL-B ™ Key Advantages:

- Superior efficacy for addressing inflammation
- Cells migrate to sites of tissue damage
- Enhanced safety as inherently Immuno-evasive
- Convenient off-the-shelf administration



Jimenez-Puerta GJ, et al. *Journal of Clinical Medicine*. 2020 Feb;9(2):445.
Mazhari R and Hare JM. *Nature Clinical Practice Cardiovascular Medicine*. 2007 Feb;4(1):S21-6.

Robust Clinical Pipeline

Indication	Geography	Phase 1	Phase 2	Phase 3	
Hypoplastic Left Heart Syndrome	U.S.				Phase 2 trial actively enrolling.
Aging-Related Frailty	U.S. & Japan				2b Single-Dose Trial complete; data announced Q3 2021. Ongoing Phase 2 trial in Japan.
Alzheimer's Disease	U.S.				Ongoing Phase 2a trial; enrollment completed; topline data anticipated by October 2023.

Lomecel-B™ for Hypoplastic Left Heart Syndrome

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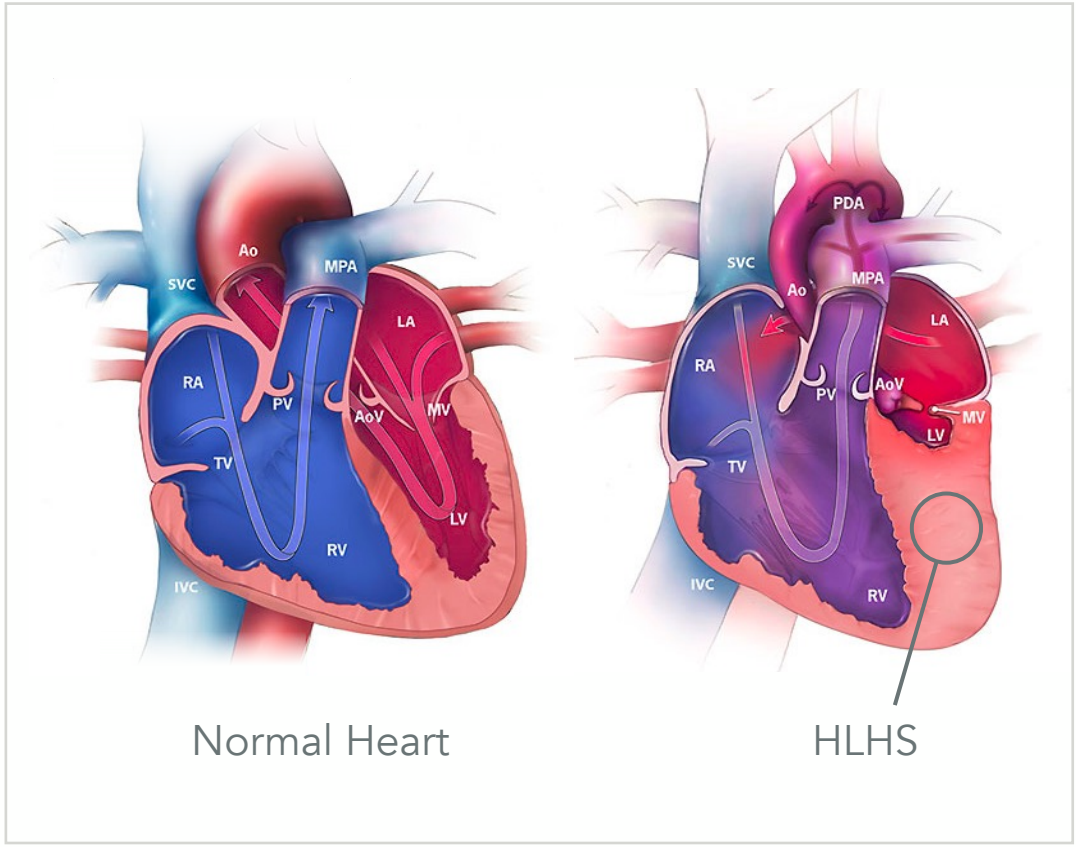
Large Unmet Need in Hypoplastic Left Heart Syndrome

- **HLHS is a rare congenital heart defect in which the left side of the heart fails to normally develop**
- **Children with HLHS require 3 staged open-heart surgeries in order to survive – these surgeries reconfigure the heart so that the right side of the heart takes over the work of the left side.**
  - Norwood Procedure – 10 days of life
  - Glenn Procedure – approximately 4 months
  - Fontan – 3-4 years
- **Even with the surgery, the overload on the RV causes it to fail and there is increased short-term mortality, delayed development, and long-term organ failure**
- **Overall survival to adolescence estimated at only 50% to 60%**
- **Affects ~1,000 babies/year in United States**



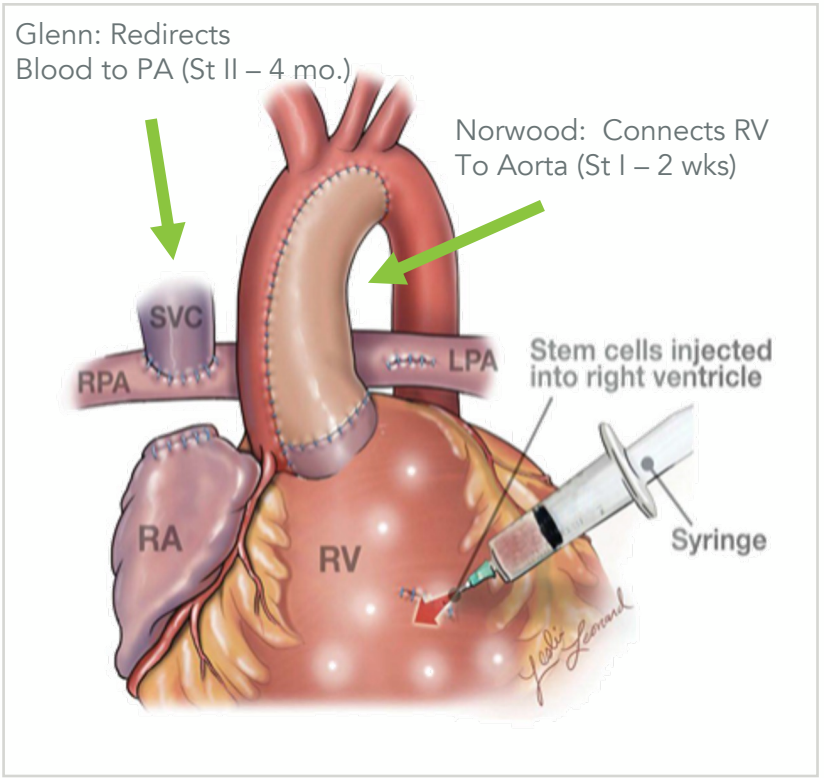
Normal Heart HLHS

Source: Abu-Harb. Arch Dis Child Fetal Neonatal Ed. 1994; Best. Front Ped. 2021; Liu. J Am Heart Assoc. 2018; Mahle. Pediatrics. 2001; Newburger. Circulation. 2018; Siffel. Pediatrics. 2015; Stasik. J Thorac Cardiovasc Surg. 2006; CDC; Children's Hospital of Philadelphia; UpToDate; ClearView Analysis.

Lomecel-B™: Hypoplastic Left Heart Syndrome (HLHS)

Clinical Approach

- **Lomecel-B™ administered directly into heart**
  - Injected into cardiac tissue of right ventricle during Stage II surgery at approximately 4 months of age ("Glenn or Hemi-Fontan Procedure")
- **Goal: To improve cardiac function through regenerative, pro-vascular and anti-inflammatory effects of MSCs**
  - Current primary endpoint is improvement in Right Ventricular Ejection Fraction (RVEF), which is a functional endpoint
    - Measured using cardiovascular magnetic resonance imaging (MRI)
    - This measure decreases over time in patients who receive Stage II surgical intervention—a good outcome would be a reduction in the magnitude of change as compared to patients who do not receive Lomecel-B ™
    - Most KOLs accept RVEF as a good functional measure of improvement due to treatment with Lomecel-B ™
- **Because of unmet need, KOLs and Payers agree that changes in RVEF as small as 5% as compared to standard of care (SOC) alone would result in treatment with Lomecel-B™ becoming SOC for HLHS**



ClearView Healthcare Partners Analysis.

Source: Derived from Bittle et al. Circulation Research (2018) 123:288-300.

Advantages of Lomecel-B™ in HLHS

- **Findings in studies of adults using MSCs:**
  - Boosts ejection fraction (EF) in patients with dilated cardiomyopathy (DCM)
    - EF increased by 8.0 percentage points (95% CI: 2.8 to 13.2 percentage points; p = 0.004)
  - Reduces ventricular chamber size in adults with DCM, an effect which would be expected to reduce valve regurgitation
    - End-diastolic long-axis diameter decreased 3.5 mm (95% CI: −6.4 mm to −0.6 mm; p = 0.04)
  - Maintains global longitudinal strain stable in babies with HLHS, one year after Stage II surgery
  - Reduces ventricular scar tissue in adults with ischemic cardiomyopathy
    - Infarct size as a percentage of LV mass declined by MSCs (-18.9%; 95% CI, -30.4 to -7.4; within-group, P = .004)

Source: Hare JM et al. *J Am Coll Cardiol* (2017) 69: 526–537; Heldman AW et al. *J Am Med Assoc* (2014) 311: 62-73; Kaushal S et al. (2022) medRxiv 2022.08.04.22278321; doi: https://doi.org/10.1101/2022.08.04.22278321

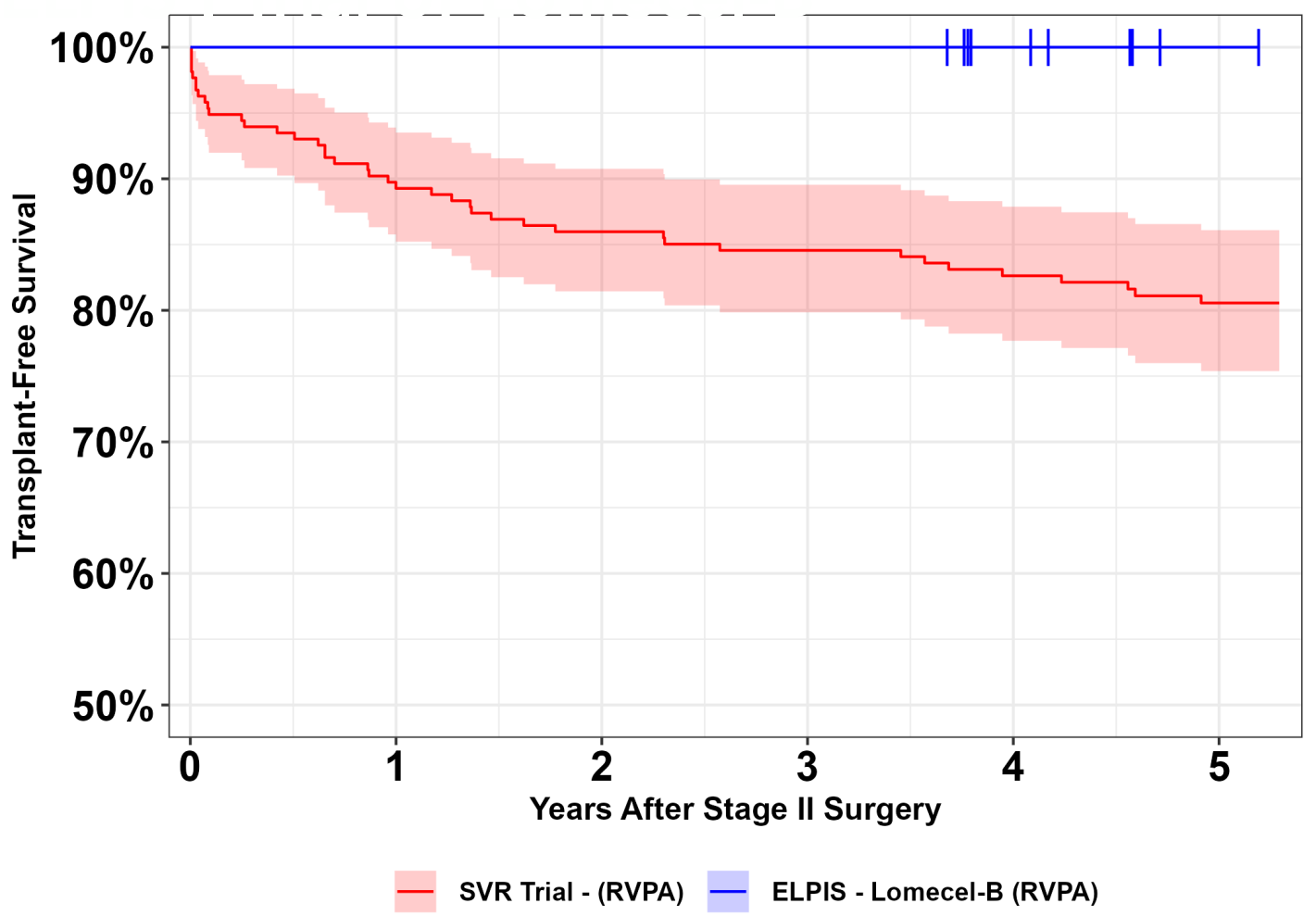
Lomecel-B™: Hypoplastic Left Heart Syndrome (HLHS)

Positive ELPIS 1 (Phase 1b) Trial Results (N=10)

- **Open-label study provided sufficient initial safety data to warrant randomized, controlled trial of Lomecel-B™ in HLHS (ELPIS II)**
  - No SAEs attributed to treatment
- **No transplants required in the 10 patients during the one year of the study duration**
  - Patients were followed beyond the initial study design parameters for a total follow-up of up to 3.5 years
- **None of the 10 treated patients required heart transplant up to 3.5 years post Stage 2 surgery***
- **Led to Rare Pediatric Disease Designation (RPD), Orphan Drug Designation (ODD) & Fast Track designations from FDA**

Published historical data (blue and red curves) adapted from Figure 2 in Son JS, et al. Circulation: Cardiovascular Imaging. 2018;11(7):e006983.
ELPIS 1 transplant-free survival data depicted in black line in graph; time since Stage II surgery and injection of Lomecel-B™ for 10 patients enrolled in the trial as of August 31, 2021.)

Long-term Survival in Hypoplastic Left Heart Syndrome (HLHS)



Results from ELPIS I trial showed 100% survival (transplant-free) In Lomecel-B™ treated patients at
up to 5 years.

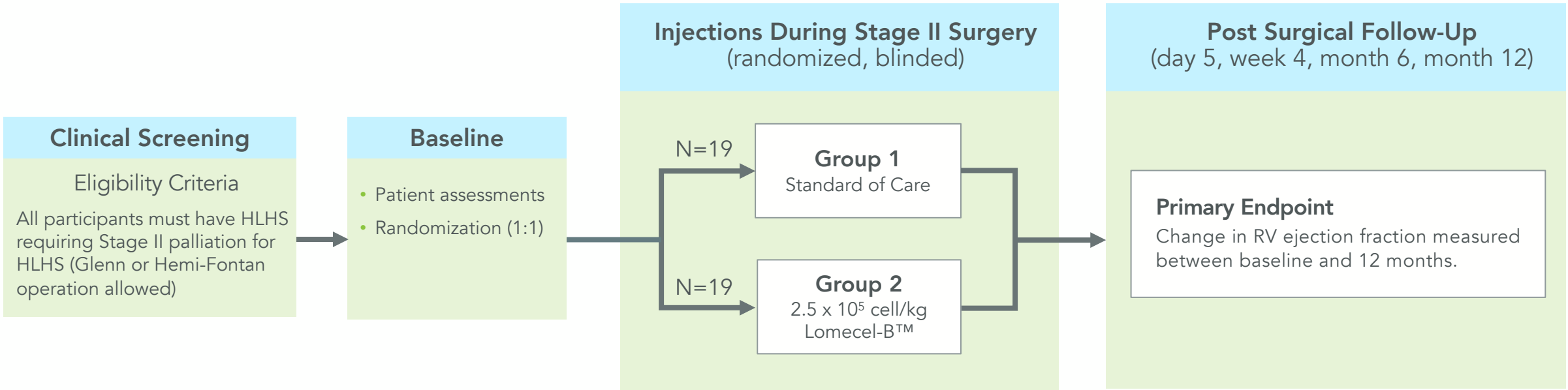
In SVR historically matched controls, 5-year mortality was ~20%

The NIH/NHLBI Pediatric Heart Network Single Ventricle Reconstruction Trial dataset was used in preparation of this work. Data were downloaded from https://www.pediatricheartnetwork.com/pud_login.asp?study_id=SVR on 05/09/2023

Lomecel-B™: Hypoplastic Left Heart Syndrome (HLHS)

ELPIS II: Ongoing Phase 2 Trial of Lomecel-B™ in HLHS

- Total population = 38 patients
- Randomized, controlled study comparing best medical care to the same treatment with addition of Lomecel-B™ (5-minute additional procedure during surgery)
- Primary endpoint: Change in Right Ventricular Ejection Fraction (RVEF) at 12 months



Lomecel-B™ for Aging-Related Frailty

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Aging-Related Frailty*: Diminishing Health, Independence and QoL

Frailty

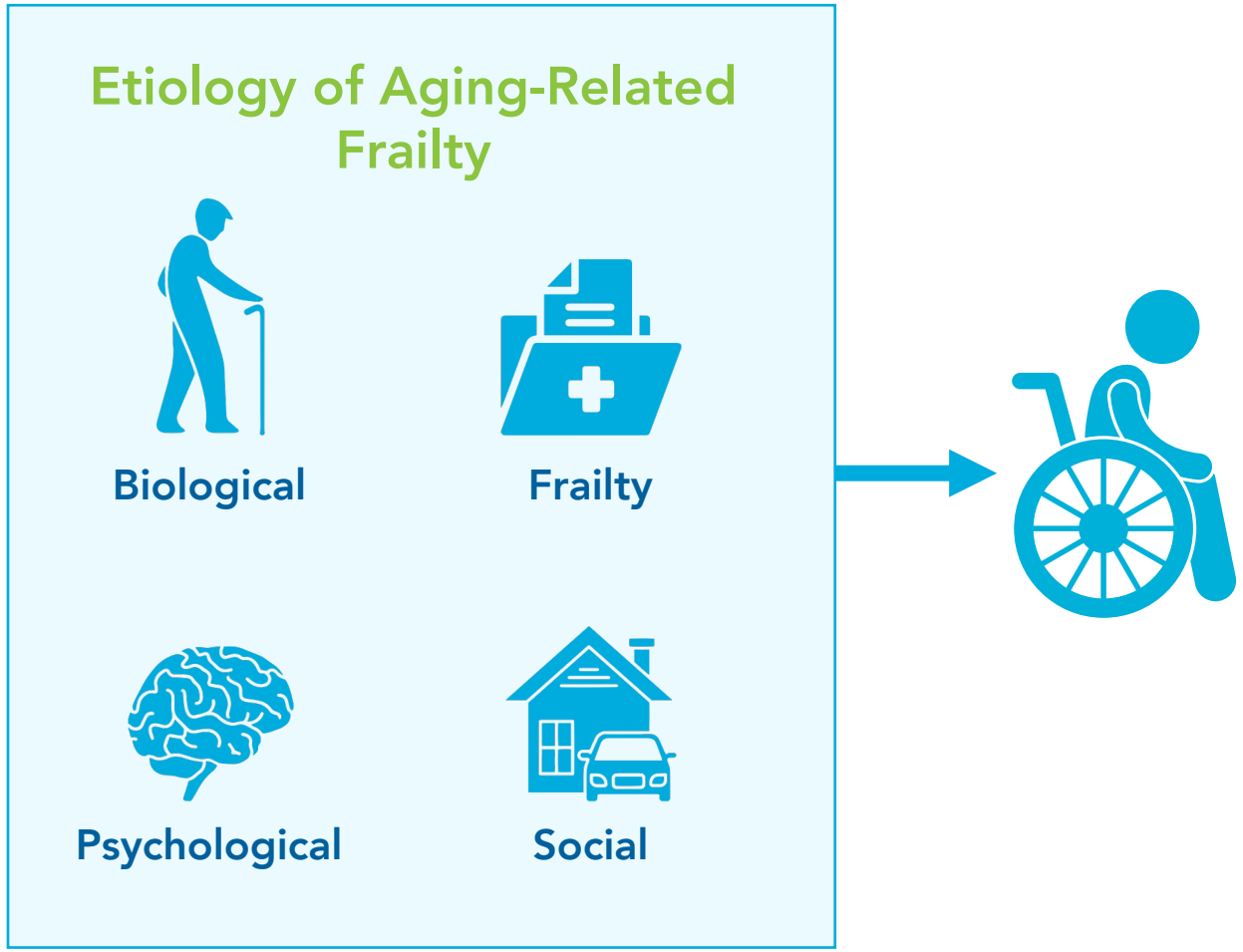
- Age-associated decline in reserve and function across multiple physiologic systems leading to inability to cope with stressors
- Characterized by mobility disability, weakness, fatigue, weight-loss, slowness, low activity, etc.

Higher risk for poor clinical outcomes

- Infections, falls, fracture, hospitalizations, death

High unmet need and high prevalence

- No approved treatments for frailty
- General prevalence of ~15% of individuals >65 using CHS Frailty Phenotype definition.[1]



[1]Bandeen-Roche K, et al. J Gerontol A *Biol Sci Med Sci.* 2015)

Adapted from Ferruci 2002.

Lomecel-B™ for Aging-Related Frailty

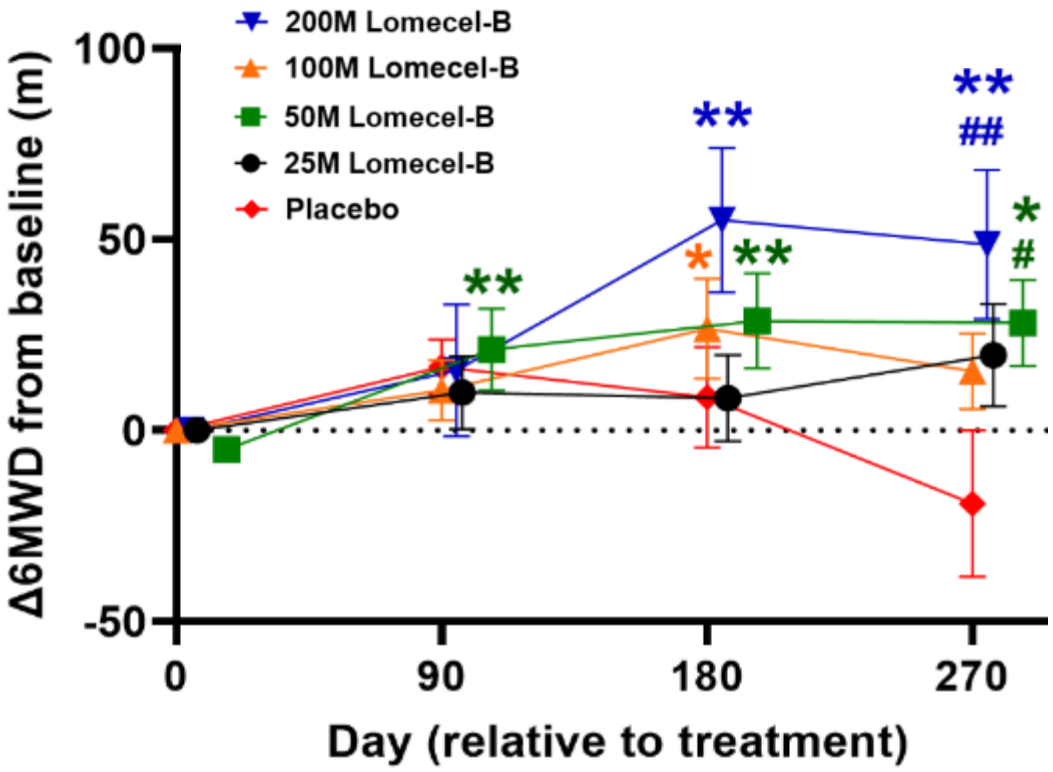
Phase 2b Study Aging-Related Frailty Study (N=143)

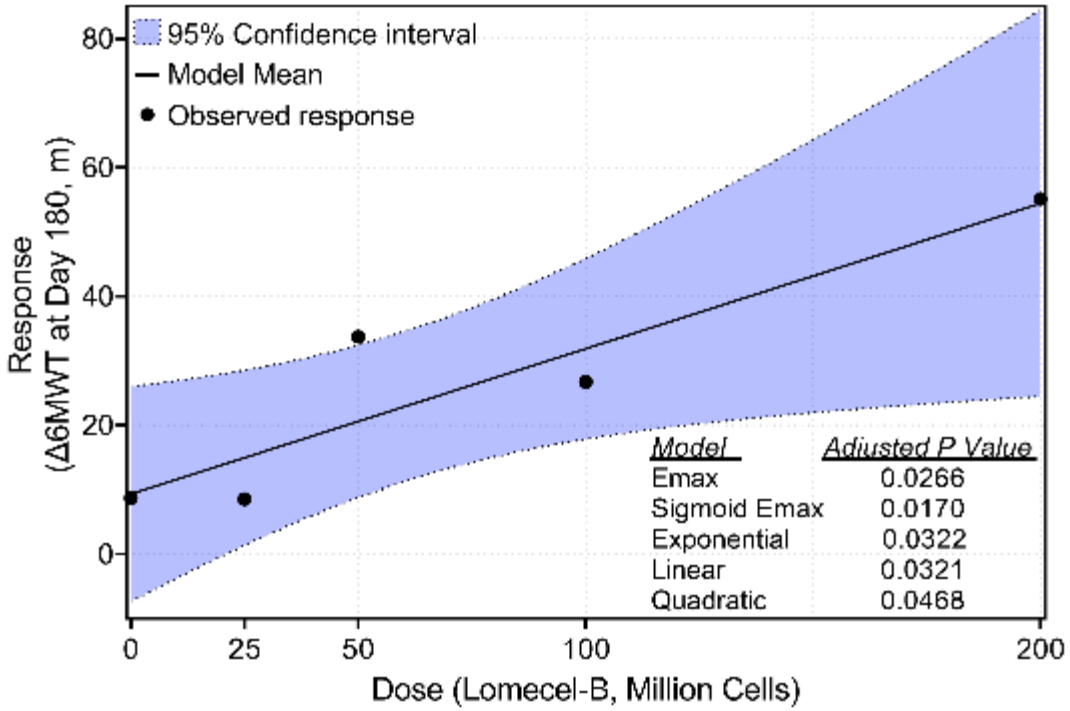
- Designed to determine whether there was a dose response to a single infusion of Lomecel-B™ in aging-related frailty
- There were 5 treatment groups: placebo and 4 different doses of Lomecel-B™: 25, 50, 100 and 200 million cells
  - Note: highest dose treatment group added after start of study
- Patients were defined as aged 70 to 85, with evidence of inflammation by elevated TNF-α levels at baseline, and with mild to moderate frailty (by CHS scale) and impaired mobility
- Primary efficacy endpoint measure was 6MWT – a test of physical endurance (distance walked in 6 minutes)

Results (graphs on next slide)

- There was a statistically significant increase in 6MWT in multiple Lomecel-B™ treatment groups 9 months after a single infusion of Lomecel-B™ compared to placebo
- There was also a dose-response to Lomecel-B™ as measured in 6MWT at 6 months
- There were no SAEs attributed to treatment with Lomecel-B™ and most AEs were related to the process of administration (associated with the insertion of a catheter for IV infusion)

Lomecel-B™ Improved 6MWT Walking Distance





Statistically-significant dose response at 180 days.

* Change from baseline; p<0.05
** Change from baseline; p<0.01

\# Versus placebo; p<0.05
\#\# Versus placebo; p<0.01

Lomecel-B™ for Aging-Related Frailty

Japan Clinical Trial Strategy Offers Fast Track for Regenerative Medicine

Regenerative Medicine (Gene and Cell Therapies)

The Act on the Safety of Regenerative Medicine (ASRM)



- Comprises all medical technologies for which the safety and efficacy have not yet been established
- Only approved for medical care and clinical research use and not intended for marketing
- Treatment at one's own expense with no insurance coverage unless part of clinical research[1]

The Act on Pharmaceuticals and Medical Devices (PMDA)



- Required for the production and marketing of regenerative and cellular therapeutic products by drug manufacturers for use nationally
- Conditional approval possible with clinical trials indicating a prediction of efficacy and assurance of safety

ASRM approval can lead to revenue generation years before BLA application with FDA or conditional approval by PMDA

[1] Will be funded by hospitals
Source: Ministry of Health, Labour and Welfare website; ClearView Analysis.

Lomecel-B™ for Aging-Related Frailty

Clinical Trial in Japan (N=45)

- Primary Objective
  - Safety
- Japanese National Center for Geriatrics and Gerontology-sponsored trial
  - NCGG (Nagoya) and Juntendo University (Tokyo) selected as clinical sites
- Amended protocol accepted by PMDA on August 8, 2022
- Ongoing Phase 2 trial



*Frailty/Aging-Related Frailty" presently does not have a consensus definition of the indication for regulatory purposes; however, it is likely that safety as observed in the proposed Phase 2 trial in Japan combined with the US Frailty 2b study will result in ASRM approval

Lomecel-B™ for Alzheimer's Disease

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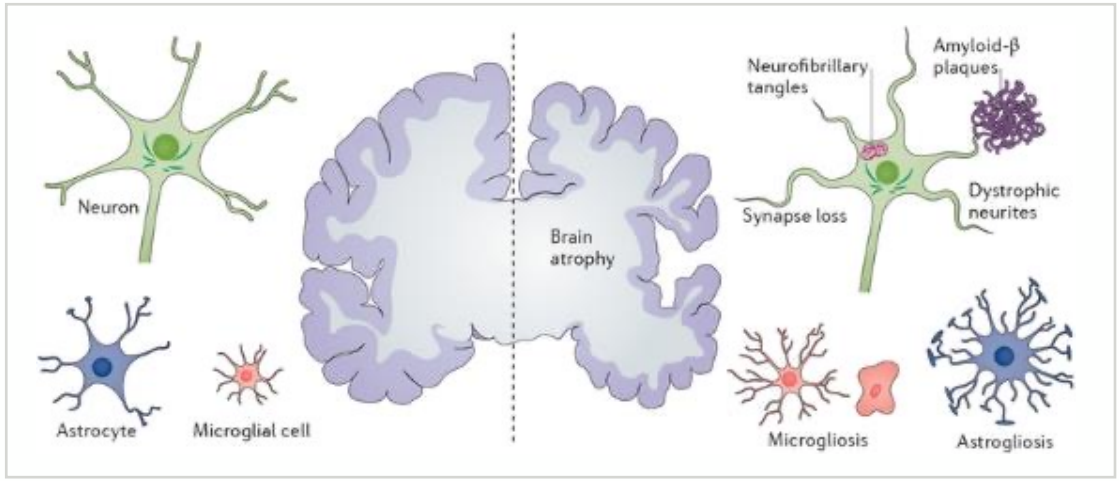
Lomecel-B™ for Alzheimer's Disease: Targeting CNS Inflammation

- Previous therapies have targeted either amyloid plaques (β-secretase inhibitors and anti-amyloid antibodies) or neurofibrillary tangles (antibodies) with little evidence of improvement of disease state
- Increasingly inflammation is recognized as a major pathway to the pathology leading to neurodegeneration in AD
- Genetic evidence for inflammation being important in AD comes from *TREM2* (an important protein in multiple immune cells) variants associated with AD*
- Inflammatory responses in brain to the pathologies of AD are increasingly recognized to drive the pathogenesis of the disease+



- MSCs effect in animal models of Alzheimer's:
  - Cross the blood brain barrier (BBB)
  - ↓ pro-inflammatory; ↑ anti-inflammatory biomarkers
  - Improve immune functioning
  - Promote neurogenesis
  - Improve endothelial function

*Shi Y, Holtzman DM (December 2018). *Nature Reviews. Immunology*. 18 (12): 759–772
+Heppner FL; Ransohoff RM; Becher B (2015).. *Nature Reviews Neuroscience*. 16 (6): 358–372

Figure from Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2018 Jul;14(7):399-415.

Lomecel-B™ for AD

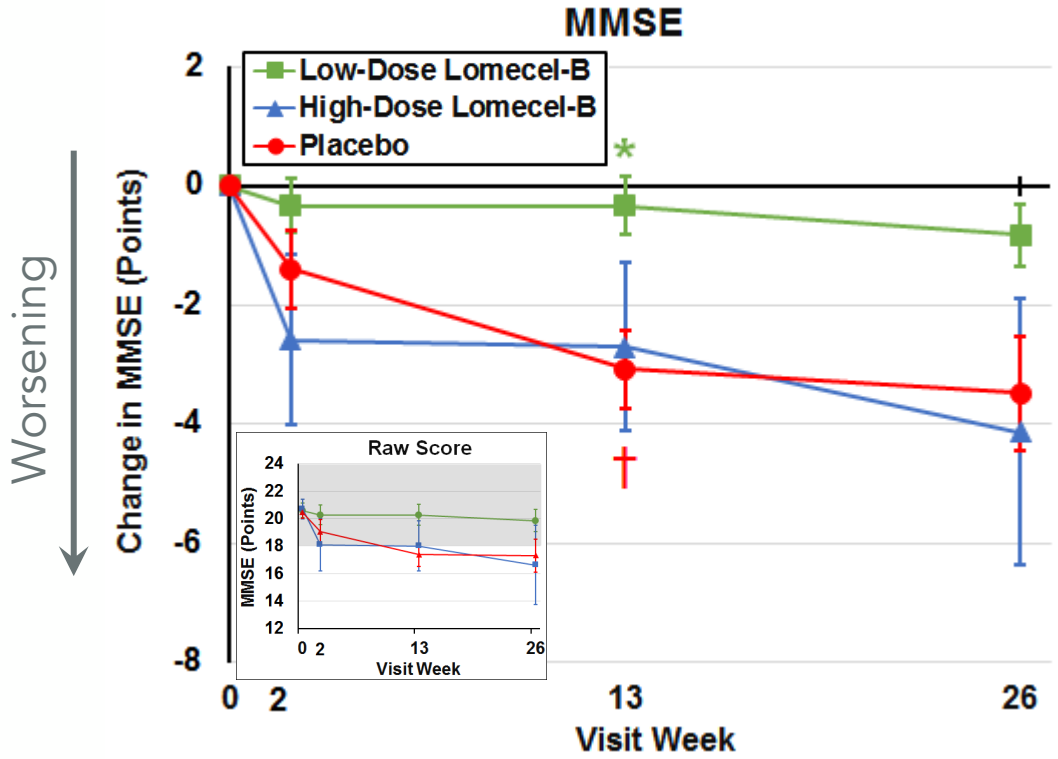
Phase 1b Randomized and placebo-controlled trial (N=33)

- Designed to study safety (primary objective) of single infusion of Lomecel-B™ in mild AD patients
  - Exploratory endpoints included cognitive measures such as Mini-Mental State Exam (MMSE)
- There were 3 treatment groups: placebo and 2 different doses of Lomecel-B™: 20 and 100 million cells
- Patients were defined by MMSE of 18-24, evidence of amyloid plaque on PET scan, and MRI to exclude other causes of cognitive impairment

Results (graphs on next slide)

- There were no SAEs attributed to treatment with Lomecel-B™ and most AEs were related to the process of administration (associated with the insertion of a catheter for IV infusion)
- There was a statistically significant improvement in cognition as measured by MMSE scores in the low-dose Lomecel-B™ group as compared to placebo and high-dose Lomecel-B™ groups
- A quality-of-life scale, QOL-AD, also seemed to indicate an improvement for patients in the low-dose Lomecel-B™ group as compared to the placebo and high-dose Lomecel-B™ groups

Low Dose Lomecel-B™: Slower Decline in cognition (MMSE) in Phase 1b Trial than placebo

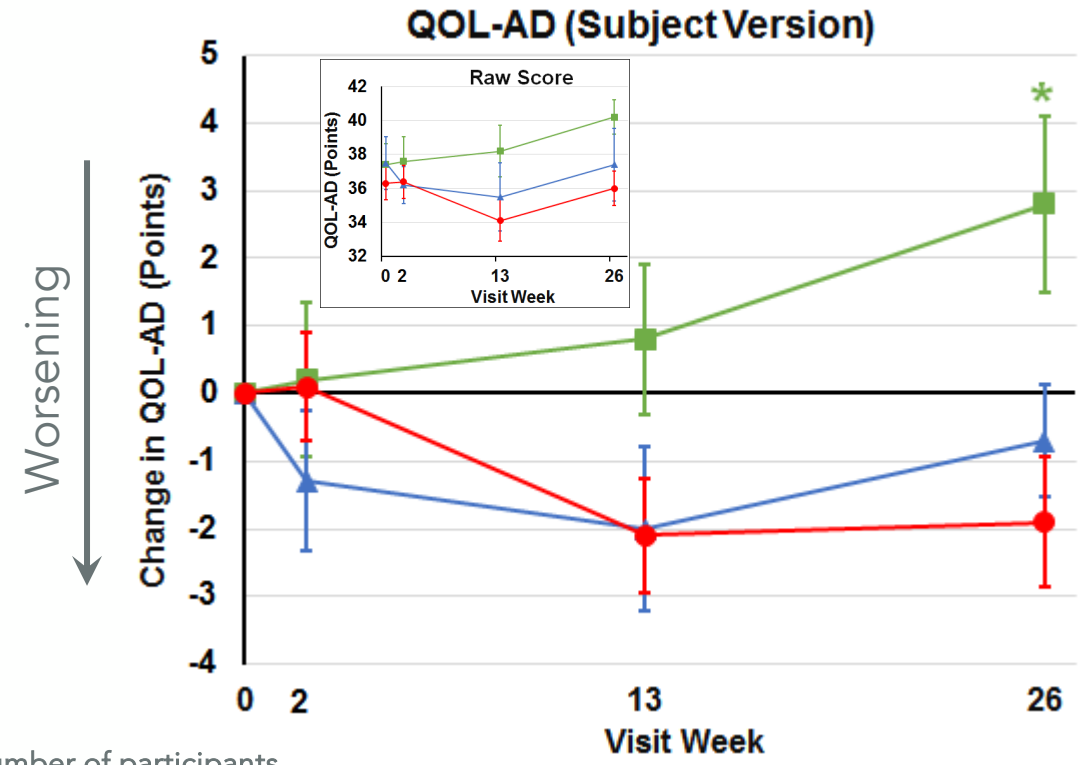


Number of participants				
Placebo	8	8	8	7
20M Lomecel-B™	15	15	15	13
100M Lomecel-B™	10	10	10	8

* 20M Lomecel-B™ compared to placebo, p<0.05

† Placebo change from baseline, p<0.05

MMSE: Mini Mental State Exam; **20M:** 20 million.



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100M Lomecel-B™	10	10	10	7

* 20M Lomecel-B™ compared to placebo, p<0.05

Phase 2a Alzheimer's Disease Study Design Ongoing

48 patients with mild AD

Treatment: 41 weeks

- **placebo**
- **single dose of Lomecel-B™**
  25 million cells
- **4 doses of Lomecel-B™**
  25 million cells
- **4 doses of Lomecel-B™**
  100 million cells

Primary Objective:
Safety

Exploratory Endpoints:
include cognitive measures such as MMSE, Clinical Dementia Rating Scale with Sum-of-boxes (CDR-SB), ADAS-Cog, biomarkers including MRI measurement of hippocampal volume, and inflammatory biomarkers

Topline data anticipated by October 2023

Designed to explore the potential efficacy of multiple doses of Lomecel-B™ in mild AD

Experienced and Successful Leadership



Wa'el Hashad

CHIEF EXECUTIVE OFFICER

- 35+ years as an executive leader in the biotechnology and pharmaceutical industries. His diverse global expertise encompasses leading early-stage companies focusing on drug approval and commercialization, as well as effectively overseeing mergers and acquisitions, and driving business development



Joshua M. Hare, MD

CO-FOUNDER & CHIEF SCIENCE OFFICER

- A pioneer and world leader in stem cell research, he is the founding director of the Interdisciplinary Stem Cell Institute at the University of Miami's Miller School of Medicine and a Fellow of various esteemed associations, including the American Heart Association and the prestigious National Academy of Inventors.



Lisa Locklear

EVP & CHIEF FINANCIAL OFFICER

- Considerable CFO and global executive leadership experience in finance and accounting at Avanir Pharmaceuticals, GSN Games, CoreLogic, Ingram Micro, the Walt Disney Company, and Price Waterhouse (now PwC). She is also a recipient of the notable Healthcare Businesswoman's Association, Luminary Award.



Nataliya Agafonova, MD

CHIEF MEDICAL OFFICER

- Extensive senior leadership experience in the biotechnology and pharmaceutical industries. Her successful cross-therapeutic expertise in drug development helped bring several products to the U.S. and EU markets.



Paul Lehr

GENERAL COUNSEL & SECRETARY

- Over 25 years of senior legal/executive roles in corporate and research settings. Former CEO of HeartGenomics, a cardiac biotech firm. Former President & General Counsel of a cardiac rehabilitation company, negotiating a master franchise agreement with 100+ facilities in India/the Middle East and securing Medicare approval with CMS.

Near-term Milestones

2023

- ✓ Full data from the Phase 1 ELPIS I trial published in the *European Heart Journal Open*
- ✓ First patient to enroll in Japan Phase 2 Aging-Related Frailty Trial
- ✓ Long-term survival data disclosed from ELPIS I trial
- Topline data from Phase 2a Alzheimer's Disease trial anticipated by October 2023

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Thank You

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U.S Market Opportunity: Large Markets with Unmet Medical Needs

	Hypoplastic Left Heart Syndrome (HLHS)	Aging-Related Frailty	Alzheimer's Disease
Patient Population	1,000[3]	8.1 million[1]	5.8 million[2]
Market Potential	Up to $1B[6]	~$4 – 8B[4]	~$5-10B[5]

[1] Company estimate based on US Census Bureau Population ≥65 years old of 54.06 million (2019 estimate) and community-dwelling Aging-Related Frailty prevalence estimates over the age of 65 (15%) from Bandeen-Roche et al; *Gerontol A Biol Sci Med Sci*. 2015. Prevalence estimates vary depending on definition criteria used and population studied.
[2] Alzheimer's Association estimate: https://www.alz.org/alzheimers-dementia/facts-figures.
[3] Centers for Disease Control and Prevention estimate. www.cdc.gov/ncbddd/heartdefects/hlhs.html
[4] Assumes 10% penetration and cost of $5,000 to $10,000 per patient
[5] Assumes 20% penetration and cost of $5,000 to $10,000 per patient
[6] Based on Market Analysis from Clearview Healthcare Partners with a wide range to acknowledge that product profile could be limited to functional cardiac improvement but might include survival benefit

Phase 2a Alzheimer's Disease Study Design (N=48) Ongoing

