Key Opinion Leader Call – April 15, 2020

Cardiac Complications of Duchenne Muscular Dystrophy
Forward-Looking Statements

Statements in this presentation release regarding the efficacy, safety, and intended utilization of Capricor's product candidates; the initiation, conduct, size, timing and results of discovery efforts and clinical trials; the pace of enrollment of clinical trials; plans regarding regulatory filings, future research and clinical trials; regulatory developments involving products, including the ability to obtain regulatory approvals or otherwise bring products to market; plans regarding current and future collaborative activities and the ownership of commercial rights; scope, duration, validity and enforceability of intellectual property rights; future royalty streams, revenue projections; expectations with respect to the expected use of proceeds from the recently completed offerings and the anticipated effects of the offerings, and any other statements about Capricor's management team's future expectations, beliefs, goals, plans or prospects constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Any statements that are not statements of historical fact (including statements containing the words "believes," "plans," "could," "anticipates," "expects," "estimates," "should," "target," "will," "would" and similar expressions) should also be considered to be forward-looking statements. There are a number of important factors that could cause actual results or events to differ materially from those indicated by such forward-looking statements. More information about these and other risks that may impact Capricor's business is set forth in Capricor's Annual Report on Form 10-K for the year ended December 31, 2019 as filed with the Securities and Exchange Commission on March 27, 2020. All forward-looking statements in this press release are based on information available to Capricor as of the date hereof, and Capricor assumes no obligation to update these forward-looking statements.

**CAP-1002 is an Investigational New Drug and is not approved for any indications. None of Capricor’s exosome-based candidates have been approved for clinical investigation.**
Call Participants

Michael Taylor, M.D., Ph.D. – Director of cardiac MR at Cincinnati Children's Hospital

Linda Marban, Ph.D. – Capricor CEO
Duchenne muscular dystrophy and the heart

Michael D. Taylor, MD, PhD
Director of cardiac MR
Duchenne muscular dystrophy and the heart

- Duchenne muscular dystrophy: Overview
- Cardiomyopathy of DMD
  - Heart muscle
  - Electrical system
  - Natural history of DMD cardiomyopathy
- Current evaluation and treatment paradigm
- Novel approaches to cardiac therapy
Duchenne Muscular Dystrophy

- *Dystrophin* mutations
- X-linked recessive
- Muscle wasting disease
- Patchy progressive fibrosis

Skeletal myopathy

Cardiomyopathy
Duchenne Muscular Dystrophy

- *Dystrophin* mutations
- X-linked recessive
- Muscle wasting disease
- Patchy progressive fibrosis
Neuromuscular diseases with cardiomyopathy

- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Other muscular dystrophies
  - Emery-Dreyfus
  - Myotonic dystrophy I
Neuromuscular diseases with cardiomyopathy

- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Other muscular dystrophies
  - Emery-Dreyfus
  - Myotonic dystrophy I

<table>
<thead>
<tr>
<th></th>
<th>DMD</th>
<th>BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystrophin protein</td>
<td>Absent</td>
<td>Partially functional</td>
</tr>
<tr>
<td>Incidence</td>
<td>1:5,000 male births</td>
<td>1:19,000</td>
</tr>
<tr>
<td>Mean age at onset, yrs</td>
<td>3-5</td>
<td>12</td>
</tr>
<tr>
<td>Mean age of becoming nonambulatory, yrs</td>
<td>~12</td>
<td>~27</td>
</tr>
<tr>
<td>Mean life expectancy, yrs</td>
<td>Mid to late 20s</td>
<td>40s</td>
</tr>
<tr>
<td>Onset of cardiomyopathy, yrs</td>
<td>16-18</td>
<td>Variable; cardiomyopathy may precede skeletal symptoms</td>
</tr>
</tbody>
</table>

BMD = Becker muscular dystrophy; DMD = Duchenne muscular dystrophy.

Circulation. 2017;136(13):e200-e231
Duchenne cardiomyopathy

- Affects 1 in 3500 males.
- Caused by dystrophin gene mutations
- Results in progressive skeletal muscle weakness.
- Results in progressive heart cell death.
- By 18, 70% have depressed heart function.

“Multifocal degenerative changes”

“Fibrosed adipose tissue”
Cardiovascular symptoms exhibited by the patient

NORMAL VENTRICULAR FUNCTION

- ECG abnormalities (Sinus tachycardia, etc.)
- Cardiomyocyte hypertrophy
- Initial diastolic dysfunction
- Wall motion abnormalities

Pre-clinical (subclinical) stage of the disease

No classic symptoms of heart failure (HF)

Window institution

0 years  10 y
Cardiovascular symptoms exhibited by the patient

- No classic symptoms of heart failure (HF)
- Minority of patients will exhibit symptoms of HF

Window of opportunity for institution of treatment

Pre-clinical (subclinical) stage of the disease

<table>
<thead>
<tr>
<th>0 years</th>
<th>10 years</th>
<th>18 - 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG abnormalities (Sinus tachycardia, etc.)</td>
<td>Cardiomyocyte atrophy</td>
<td></td>
</tr>
<tr>
<td>Cardiomyocyte hypertrophy</td>
<td>Subendocardial fibrosis</td>
<td></td>
</tr>
<tr>
<td>Initial diastolic dysfunction</td>
<td>Progressive dilatation of heart chambers</td>
<td></td>
</tr>
<tr>
<td>Wall motion abnormalities</td>
<td></td>
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</tr>
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</table>

NORMAL VENTRICULAR FUNCTION
Cardiovascular symptoms exhibited by the patient

- No classic symptoms of heart failure (HF)
- Minority of patients will exhibit symptoms of HF
- About 60% of patients will exhibit symptoms of HF, palpitations, syncope

Window of opportunity for institution of treatment

Pre-clinical (subclinical) stage of the disease
- 0 years
- NORMAL VENTRICULAR FUNCTION
  - ECG abnormalities (Sinus tachycardia, etc.)
  - Cardiomyocyte hypertrophy
  - Initial diastolic dysfunction
  - Wall motion abnormalities

Clinical stage of the disease
- 10 years
- Cardiomyocyte atrophy
- Subendocardial fibrosis
- Progressive dilatation of heart chambers

Detectable cardiac involvement
- 18 - 20 years
- Systolic dysfunction
  - Dilated cardiomyopathy
  - Arrhythmic complications

END-STAGE HEART FAILURE
- Death due to HF usually occurs between ages 20 to 40
  - HF is the cause of up to 40% of deaths in patients with DMD

80% to 100% of patients will have detectable signs of cardiac dysfunction in this stage

Survival by era

**SS → spine surgery**

Survival by era

![Bar chart showing age at death by era]

- Vent 50s
- Vent 1990s
- Died 1990s
- Died 1980s
- Died 1970s
- Died 1960s

**SS ➔ spine surgery

*(Neuromuscular Disorders. 2002;12(10):926-929.)*

Survival by era

**SS ➔ spine surgery**


50%

~27 y
Ambulatory Monitoring and Arrhythmic Outcomes in Pediatric and Adolescent Patients With Duchenne Muscular Dystrophy

Chet R. Villa, MD; Richard J. Czosek, MD; Humera Ahmed, MD; Philip R. Khoury, MS; Jeffrey B. Anderson, MD; Timothy K. Knilans, MD; John L. Jeffries, MD; Brenda Wong, MD; David S. Spar, MD

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>EF ≥5%</th>
<th>EF 54% to 35%</th>
<th>EF &lt;35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td>235</td>
<td>184</td>
<td>46</td>
<td>5</td>
</tr>
<tr>
<td>Number of Holters, n</td>
<td>442</td>
<td>337</td>
<td>95</td>
<td>10</td>
</tr>
<tr>
<td>Significant Holter finding, n (%)</td>
<td>12 (3)</td>
<td>4 (1)</td>
<td>4 (4)</td>
<td>4 (40)</td>
</tr>
</tbody>
</table>

% significant arrhythmias

- Total: 3
- Normal function: 1
- Mild - moderate dysfunction: 4
- Severe dysfunction: 40
Why cardiac MR?
Cardiac MR in Duchenne

- Replaces echocardiogram after age 6-8
- Patients undergo yearly exams
- No sedation
- Typical exam ~30 minutes
- Abbreviated non-contrast version ~10 minutes
- 2238 exams since 2004
Cardiac MR findings

Cardiac function – advanced disease

Late gadolinium enhancement ("LGE")
DMD cardiomyopathy – natural history


DMD cardiomyopathy – natural history


Myocardial Fibrosis Burden Predicts Left Ventricular Ejection Fraction and Is Associated With Age and Steroid Treatment Duration in Duchenne Muscular Dystrophy

Animesh Tandon, MD, MS; Chet R. Villa, MD; Kan N. Hor, MD; John L. Jeffries, MD, MPH; Zhigian Gao, PhD; Jeffrey A. Towbin, MD, MS; Brenda L. Wong, MD; Wojciech Mazur, MD; Robert J. Fleck, MD; Joshua J. Sticka, MD; D. Woodrow Benson, MD, PhD; Michael D. Taylor, MD, PhD

Therapies – current evidence

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Level of Evidence</th>
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<tr>
<td>Corticosteroids</td>
<td>++</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>+++</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>+</td>
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<td>Mineralocorticoid receptor antagonists</td>
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ACE = angiotensin-converting enzyme; DMD = Duchenne muscular dystrophy.
Therapies – current evidence

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Steroids

Therapies – current evidence

Steroids

![Graph showing overall survival with and without steroid therapy.](image)

**Level of Evidence**

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Therapies – current evidence

ACE inhibitors

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Am J Cardiol. 2006;98(6):825-827.
Therapies – current evidence

Mineralocorticoid receptor antagonists

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ACE = angiotensin-converting enzyme; DMD = Duchenne muscular dystrophy.


Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial

Subha V Raman, Kan N Hor, Wojciech Mazur, Nancy J Halnon, John T Kissel, Xin He, Tam Tran, Suzanne Smart, Beth McCarthy, Michael D Taylor, John L Jefferies, Jill A Rafael-Fortney, Jeovanna Lowe, Sharon L Roble, Linda H Cripe

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular strain, %</td>
<td>0.84% (2.68)</td>
<td>0.38% (2.56)</td>
<td>0.602</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>0 (-3.8 to 4.0)</td>
<td>1.0% (-5.0 to 2.1)</td>
<td>0.474</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>1.50 (14.35)</td>
<td>0.87 (13.70)</td>
<td>0.893</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>1.4 (-4.5 to 6.6)</td>
<td>1.7 (-2.9 to 3.6)</td>
<td>0.915</td>
</tr>
<tr>
<td>LGE, % of left ventricular mass</td>
<td>-2% (6)</td>
<td>4% (6)</td>
<td>0.034</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin-I, ng/mL</td>
<td>0 (-0.01 to 0.01)</td>
<td>0 (-0.02 to 0.01)</td>
<td>0.840</td>
</tr>
<tr>
<td>Total creatine kinase, U/L</td>
<td>-590 (-1868 to 4)</td>
<td>-520 (-3156 to 1205)</td>
<td>0.589</td>
</tr>
<tr>
<td>Creatine kinase MB, %</td>
<td>0.19% (1.52)</td>
<td>0.13% (1.68)</td>
<td>0.616</td>
</tr>
<tr>
<td>Osteopontin, ng/mL</td>
<td>-13.25 (42.12)</td>
<td>-11.06 (33.56)</td>
<td>0.859</td>
</tr>
</tbody>
</table>

Data are mean (SD) or median (IQR). LGE= late gadolinium enhancement. EDV=end-diastolic volume. ESV=end-systolic volume.
Capricor’s CAP-1002 Technology

CAP-1002 is a biologic consisting of allogeneic cardiosphere-derived cells (CDCs)

- Manufactured from donated heart muscle
- Does not act by “stemness” - the cells do not engraft into host tissue
- Mechanism: cells secrete exosomes:
  - Contain miRNA, non-coding RNAs and proteins
  - Internalized by target cells
  - Stimulate diverse and lasting changes in cellular behavior
  - 3 known miRNAs drive CAP-1002 potency
- CAP-1002 has been investigated in multiple independent clinical trials and more than 150 human subjects to date
HOPE-Duchenne Focused on Older DMD Patients

• Phase I/II study: 25 patients, randomized and open-label
• One-time, multi-vessel, intracoronary delivery of cells
• HOPE population were all on stable corticosteroids
• Very limited options for this patient population

RESULTS
• Reduction in cardiac scar at 6 and 12 months measured by MRI
• Improvement in cardiac function (systolic wall thickening) at 6 and 12 months
• Improvements shown in PUL (mid + distal)
  – Best improvement shown within the first 3 months
• Study published in February 2019 in Journal of Neurology

https://n.neurology.org/content/92/8/e866
Study funded with the support of CIRM https://clinicaltrials.gov/ct2/show/NCT02485938.
HOPE-Duchenne: Reduced Cardiac Scar and Improved PUL

HOPE-2 Clinical Trial

- **Design**: Phase II, randomized, double-blind, placebo-controlled trial in participants with DMD and reduced skeletal muscle function
- **Objective**: Evaluate safety and efficacy of CAP-1002
- **Dosing Regimen**: 150M cells delivered intravenously every 3 months
- **Sites**: 9 sites (USA)
- **Interim Analysis**: ITT population - 20 subjects
- **Demographics**
  - Mean age: 14.3 years
  - All patients were on corticosteroids
  - ~80% of patients were non-ambulant

Advanced heart failure therapies

• 2019 study of 43 DMD patients with severe dysfunction
• Ventricular assist device – 4
• Heart transplant – 1

<table>
<thead>
<tr>
<th>Device implanted</th>
<th>Goal of LVAD*</th>
<th>Home on device</th>
<th>LVAD* complication (months from implant)</th>
<th>Alive as of 1/1/2018 (mo from implant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeartWare</td>
<td>Destination therapy</td>
<td>Yes</td>
<td>Yes, pump thrombosis (16)</td>
<td>Yes, with device (18)</td>
</tr>
<tr>
<td>HeartMate II</td>
<td>Bridge to transplant</td>
<td>Yes</td>
<td>No</td>
<td>No, deceased (5)</td>
</tr>
<tr>
<td>HeartMate II</td>
<td>Destination therapy</td>
<td>Yes</td>
<td>Yes, gastrointestinal bleed (10)</td>
<td>Yes, heart transplant (10)</td>
</tr>
<tr>
<td>HeartWare</td>
<td>Bridge to decision</td>
<td>Yes</td>
<td>Yes, stroke (5)</td>
<td>No, deceased (5)</td>
</tr>
</tbody>
</table>

Selected characteristics of Duchenne muscular dystrophy cases with severe Left Ventricular Systolic Dysfunction

<table>
<thead>
<tr>
<th>Died during study period (N = 12)</th>
<th>Alive at study end (N = 29)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at death/study end</td>
<td>median (IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20.8 (IQR 15.9-24.6)</td>
<td>19.6 (IQR 17.0-22.1)</td>
</tr>
<tr>
<td>Median age ambulation ceased</td>
<td>median (IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (IQR 9-12)</td>
<td>11 (IQR 10-13)</td>
</tr>
<tr>
<td>Current/past steroid use</td>
<td>median (IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (50%)</td>
<td>22 (75.9%)</td>
</tr>
<tr>
<td>Heart failure admission</td>
<td>median (IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (41.7%)</td>
<td>7 (24.1%)</td>
</tr>
<tr>
<td>VAD implanted</td>
<td>median (IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (8.3%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>ICD implanted</td>
<td>median (IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>Medication use at last cardiac evaluation</td>
<td>median (IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10/11 (90.9%)</td>
<td>28/31 (90.3%)</td>
</tr>
<tr>
<td></td>
<td>Ace-inhibitor/angiotensin Receptor Blocker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7/11 (63.6%)</td>
<td>20/31 (64.5%)</td>
</tr>
<tr>
<td></td>
<td>Beta-Blocker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6/11 (54.5%)</td>
<td>18/31 (58.1%)</td>
</tr>
<tr>
<td></td>
<td>Ace-inhibitor/Receptor Blocker + Beta-Blocker</td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic strategies

DMD gene mutation → Abnormal dystrophin protein → Dysfunction of sarcolemmal stretch-activated ion channels → Release of enzymes into bloodstream → Serum CK values

DAPC destabilization → Sarcolemmal permeability →↑ entry of extracellular Ca^{2+}

Degradation of contractile proteins →↑ increased release of Ca^{2+} from intracellular stores

Activation of Ca^{2+} - induced proteases

Inflammatory response → Fibrosis formation → Stretch and thinning of fibrotic region → Cardiomyocyte death and apoptosis

Heart failure → Left ventricular volume → Wall stress → Diastolic relaxation

Mitochondria dysfunction

Correcting perturbations in Calcium handling

Correcting blood flow regulation

Replacement of dystrophin/utrophin

Increasing muscle mass and regeneration

Decreasing inflammation and fibrosis

Courtesy of Craig McDonald, MD
Summary

• Duchenne associated cardiomyopathy is an inexorably progressive disease with variable onset.
• Current therapies provide marginal therapeutic benefit.
• These patients need a transformative therapy that prevents the replacement of cardiac muscle cells or provides new muscle cells.
Thank you

Question and Answers

info@capricor.com
Cardiac magnetic resonance group

Cardiology
Michael Taylor, MD, PhD
Tarek Alsaied, MD
Sean Lang, MD
Ryan Moore, MD
Justin Tretter, MD

Radiology
Eric Crotty, MD
Rob Fleck, MD
Manu Rattan, MD

Physics
Amol Pednekar, PhD
Jean Tkach, PhD
LGE → What is it really showing?

- Collagen replacement
- Gross fibrosis
- Protein infiltration
- Myocardial disarray
- Fine interstitial fibrosis without disarray

Circumferential Strain Analysis Identifies Strata of Cardiomyopathy in Duchenne Muscular Dystrophy

A Cardiac Magnetic Resonance Tagging Study

Kan N. Hor, MD,* Janaka Wansapura, PhD,† Larry W. Markham, MD,‡ Wojciech Mazur, MD,§ Linda H. Cripe, MD,* Robert Fleck, MD,† D. Woodrow Benson, MD, PhD,* William M. Gottliebson, MD*