Carmeseal-MD® (P-188 NF) for the treatment of cardiac & respiratory dysfunction in DMD

Upcoming Clinical Trial P-004 NCT03558958
PPMD Annual Meeting, 30 June 2018
THIS IS NOT AN OFFER TO SELL SECURITIES. Information provided in this presentation is not, and should not be construed as, an offer to sell securities or the solicitation of an offer to buy securities, nor shall there be any sale of securities by Phrixus pursuant to this presentation in any jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration, exemption, or qualification under the securities laws of such jurisdiction.

Information herein is believed, but not guaranteed, to be reliable, accurate and complete. Any opinions or estimates expressed herein reflect a judgment made as of this date and are subject to change. Phrixus is not making any representations, warranties, or guarantees with respect to the information contained herein.
Phrixus – An entrepreneurial specialty pharma company with orphan drug focus

Mission
Advancing Carmeseal™ for Duchenne Muscular Dystrophy (DMD) and other diseases caused by membrane instabilities

Two initial product candidates based on Carmeseal (P-188 NF) poloxamer technology

- Carmeseal-MD™: Formulation for DMD - daily subcutaneous dosing similar to insulin
- Carmeseal-HF™: Formulation for acute decompensated heart failure

Long-standing collaboration with Cincinnati Children’s regarding DMD product candidate Carmeseal-MD

Ready to test Carmeseal-MD (P-188 NF) in trial P-004, its first Proof-of-Concept trial in Duchenne muscular dystrophy
DMD – A degenerative disease with unmet clinical needs that go beyond loss of ambulation

15,000 to 20,000 boys and young men affected by DMD in US and Europe each

Increasing life span apparently shifting patient mix to non-ambulatory patients, now estimated at 60% of patient population. However, these patients also suffer from heart failure

There are no device options for heart failure: “There is no wheel chair for the heart” (Dr. Jeffery Towbin)
DMD – A degenerative disease whose leading cause of death is now heart failure

Patient journey after diagnosis at age 2-7

- Increasing skeletal muscle weakness
- Increasing respiratory dysfunction
- Development of clinical symptoms of heart disease

Increasing role of heart failure
- 25% of DMD patients have sub-clinical signs by age 6
- Annual screening by echocardiography recommended starting at age 10
- Cardiac involvement in 90% of patients by age 18, important factor not only in DMD but also Becker MD and mothers who are “carriers”
- Standard heart failure therapies inadequate
Heart failure in DMD – Difficult-to-treat disease with no endpoint guidance from regulators

- Different muscles responding differently (or not at all) to current therapeutics
- Compounds in clinical development have limited efficacy against heart disease
- FDA does not accept imaging as approvable endpoint, so you need more than cardiac imaging for approval of any product targeting heart failure
- FDA Guidance highlights that new therapies that improve ambulation will also further strain and put at risk clinically vulnerable hearts
Carmeseal-MD development strategy combines science with regulatory compliance

Develop Carmeseal-MD (P-188 NF) as a therapeutic agent against both respiratory dysfunction and heart failure.

Respiratory endpoints will support approval and cardiac endpoints will support use against heart failure (“pull through” or “coattail approach”).

Approach fully leverages preclinical efficacy data, previous human experience and FDA guidelines.
Carmeseal-MD (P-188 NF) – This First-in-Class therapeutic agent acts as membrane sealant

- Acts as a molecular band-aid – Addresses membrane instabilities (“tears”) and membrane failure
- Addresses underlying disease pathology rather than symptoms, acts as disease modifying agent (DMT)
- Broadly applicable – Not limited to specific mutation like gene therapy product candidates, better effects on diaphragm and heart
- Likely additive to other therapies due to unique and novel mechanism of action, therefore suitable for combination therapeutic (if combination needed)
Carmeseal-MD (P-188 NF) is attractive because of its amphiphilic structure ...

where $a \approx 80$ and $b \approx 27$
… which allows for repair of membrane instabilities ("tears") that characterize muscle cells in DMD – Mechanism of action

Note: Nature 2005: 436: 1025-1029
Carmeseal- MD – Strong effects along relevant dimensions in several pre-clinical *in vivo* models

Cardiac: Muscle function improved in 4 models of HF including *mdx* mouse and GRMD dog models of DMD. Strong functional data. Shown in GRMD dog model and in *mdx* mice to prevent remodelling

Respiratory: Shown in two mouse models of DMD to prevent deterioration of respiratory endpoints

Fibrosis: Shown to prevent fibrosis with magnitude of effect similar to steroids

Skeletal limb muscle: Shown to have positive effects when administered subcutaneously (as in Phrixus’s programs)
In addition, two patients were on Carmeseal-MD for 16 and nine months, respectively

**Patient 1 (Argentina)**
- 13 years old, non-ambulatory, treatment triggered by declining respiratory function
- Started on dose of 5 mg/Kg once-a-day subcutaneous, then escalated to 10 mg/Kg (family’s decision)
- 60% reduction in creatine kinase after eight weeks of dosing at lower dose – Appr. 2,500 U/L down to 1,061 U/L (CK reduction at 10 mg/Kg & cardiac troponin T NA), further reduction to 800 U/L
- Well-tolerated

**Patient 2 (New Zealand)**
- 23 years old, non-ambulatory with cardiac and respiratory dysfunction
- Dose of 5 mg/Kg once-a-day subcutaneous
- 21% reduction in cardiac troponin T after 12 weeks (hsTroponinT from 52 ng/L to 41 ng/L)
- CK levels dropped from 152 U/L to 142 U/L.
- Well-tolerated

Notes: Provided via Ethicor Pharma, UK, manufactured in the UK under unlicensed specials rules
The first trial P-004 is a Phase 2 Proof-of-Concept trial

**Primary endpoint**
- Forced Vital Capacity (FVC) as primary endpoint

**Secondary endpoints**
- PCF, PEF, FEV-1, TV and PIF
- LVEDV, EF, degree of fibrosis, IVRT, wall strain
- PUL, cardiac troponin I, muscle creatine kinase, PK

**Exploratory endpoints**
- MIP, MEP, hospitalizations for respiratory causes, serious respiratory infections, time to tracheostomy, OSA, others
- Systolic/diastolic function, cardiac mass, RVV and remodeling
- Quality of life per PedsQL

**PoC trial with eight non-ambulatory patients with DMD at Cincinnati Childrens**
- Open-label trial for 52 weeks
- Single once-a-day dose of 5 mg/Kg of P-188 NF
- Steroid users and non-users as long as stable
- Dr. Thomas Ryan and Dr. John Jefferies as PIs

Clinicaltrials.gov NCT03558958
Selected inclusion criteria: Initial focus on non-ambulatory boys and young men (1/2)

- Be male;
- Be 12 - 25 years of age (18-25 years of age for first group of three);
- Have impaired respiratory function (percent predicted FVC ≤80%);
- Have ability to perform repeat PEF within 15% of first assessment;
- Have mild or moderate fibrosis of the heart, as assessed by MRI;
- Have left ventricular ejection fractions of <50% when measured by both MRI and echo;
- Have been non-ambulatory for at least six months (non-ambulation defined as participant in wheelchair for all ambulation, even at home);
Selected inclusion criteria: Initial focus on non-ambulatory boys and young men (2/2)

- Be on corticosteroids, with a stable treatment regimen for at least six months;
- Have been on a stable treatment regimen for cardiac dysfunction for at least 3 months prior to baseline (treatments defined as ACE inhibitors, beta blockers and/or ARBs); Spironolactone is allowed but patient must be on a stable dose for 6 months prior to enrollment; and
- Must reside within 200 miles of Cincinnati Children’s Hospital Medical Center and be able and willing to travel to CCHMC for clinic and blood draw visits.
Selected exclusion criteria (1/2)

- Exposure to another investigational drug within 90 days prior to start of study treatment except for Deflazacort;
- Percent Predicted FVC < 55%;
- Are unable to perform pulmonary function testing;
- Have respiratory failure (defined as requiring ventilation during awake time);
- Are unable or unwilling to undergo echocardiography or MRI with gadolinium as contrast agent;
- Have severe fibrosis of the heart as assessed by MRI;
- Used certain supplements within 30 days prior to screening;
- Have a history of major surgical procedure within 30 days prior to start of study treatment;
Selected exclusion criteria (2/2)

• Have ongoing immunosuppressive therapy (other than corticosteroids);
• Are participating in a therapeutic clinical trial (except for the Deflazacort Expanded Access Program);
• Have a diagnosis of chronic lung disease including asthma and cystic fibrosis or the presence of any other non-DMD respiratory illness that affects PEF;
• Are chronic users of beta-2 agonists or other bronchodilating medications in the preceding 1 month; and
• Have moderate or severe hepatic impairment or moderate to severe renal impairment as determined by the Principal Investigator.
Summarizing Carmeseal-MD

A unique approach based on solid science and with great promise to treat heart failure and respiratory dysfunction in boys and young men with DMD

Potential to address multiple aspects of the disease, not just heart disease, so no change in FDA’s policy is required to get approval

First trial is already Phase 2 trial, so timeline to approval is shortened

National Institutes of Health and parent organizations have been crucial in getting this approach towards its first clinical trial
Phrixus’s pre-clinical work was supported by NIH and economic development agencies
This clinical program at Phrixus and CCHMC is supported by several parent organizations
Relevant contact information

**Clinicaltrials.gov:** NCT03558958

**Contact at Cincinnati Children’s Hospital Medical Center regarding enrollment:**
info_carmeseal@cchmc.org

**Dr. John Lynn Jefferies**
John.Jefferies@cchmc.org

**Dr. Thomas A. Ryan**
Thomas.Ryan@cchmc.org

**Thomas A. Collet**
thomas.collet@phrixuspharmaceuticals.com
Backup slides
<table>
<thead>
<tr>
<th><strong>Phrixus developing Carmeseal-MD (P-188 NF) against cardiac and respiratory dysfunction in DMD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>A multi-factorial disease in which different muscles respond differently to therapies under development - Efficacy against heart muscle is lacking</td>
</tr>
<tr>
<td>No practical FDA guidance for approval of HF therapies, so these therapies need to be approved on the basis of other benefits (“pull-through” or “coattail strategy”)</td>
</tr>
<tr>
<td>Carmeseal-MD (P-188 NF) with novel mechanism of action (membrane sealant) has shown robust respiratory and cardiac benefits in animal models</td>
</tr>
<tr>
<td>Phrixus and Cincinnati Children’s collaborating on eight patient trial to demonstrate benefits on respiratory and cardiac dysfunction</td>
</tr>
<tr>
<td>Approval would be based on forced vital capacity (respiration), primary therapeutic effect would be cardiac (managed by cMRI)</td>
</tr>
<tr>
<td>Trial funded by multiple parent organizations</td>
</tr>
</tbody>
</table>
P-188 NF targets the primary defect – Membrane instability resulting from loss of dystrophin

MoA HYPOTHESIS – STRUCTURAL PERSPECTIVE

Generally known & accepted?

- Dystrophin is an essential structural membrane protein
- DMD renders dystrophin non-functional
- Primary defect: Lack of functional dystrophin leads to structurally dysfunctional membrane and instability / tears
- Membrane instabilities and tears cause a number of secondary effects

Supportive findings (selected publications starting in 1975)

Chronic effects: P-188 NF prevents dilated cardiomyopathy in the GRMD dog model of DMD

Golder retriever dog model of muscular dystrophy

Prevents dilation - Maintains normal relaxation - Prevents fibrosis - No renal or liver safety signals after 60 day IV administration

Note: Done at University of Minnesota and University of Michigan
Carmeseal-MD™ significantly improves respiratory function in a mouse model of DMD

**Respiratory studies mdx mouse**

**Effects of P-188 NF and prednisone on tidal volume/BW in the mdx mouse over time.** *Mdx* mice were treated QD, s.c. with P-188 NF (3 mg/Kg) or prednisone (1 mg/Kg) from age 7 months to 12 months ±2 weeks. The black line represents wild-type mice (C57BL/10 SnJ) treated with saline. The red line represents *mdx* mice treated with saline. The blue line represents mice treated with P-188 NF (Panel A) or 1 mg/Kg prednisone (Panel B). Data points are means +/- S.D. N=11 for *mdx* 3 mg/Kg P-188 NF at 20 and 22 weeks, N=12/group for prednisone treatment.

**Panel A**, $P<0.0001$ for the overall effect of P-188 NF 3 mg/Kg group vs. *mdx* saline and wild type saline. The *mdx* 3 mg/Kg group was also significantly greater than *mdx* saline at 22 weeks ($P<0.0001$).

**Panel B**, $P=0.001$ to 0.0001 for *mdx* 1 mg/Kg prednisone group vs. *mdx* saline and $P<0.0001$ vs. wild type saline. The *mdx* prednisone group was also significantly greater than *mdx* saline at 22 weeks ($P<0.0001$).

Carmeseal-MD™ significantly reduces fibrosis in \textit{mdx} mice

Respiratory studies \textit{mdx} mouse

Fibrosis of diaphragm muscle from 1-year-old \textit{mdx} and wild type control mice after 22 weeks of treatment with saline or P-188 NF. Sections of diaphragms from the same groups of mice described above were stained with Picosirius Red to visualize collagen deposition. All staining was done on diaphragm muscle from 12-month old mice with the exception of Panel B. Shown in the figure are cross sections of diaphragm muscle from: Panel A, wild type control saline-treated mouse; Panel B, a 7 month old \textit{mdx} mouse; Panel C, and \textit{mdx} saline-treated mouse; Panel D, and \textit{mdx} mouse treated with 3 mg/Kg P-188 NF; Panel E, and \textit{mdx} mouse treated with 1 mg/Kg prednisone.

In the *mdx* mouse model, P-188 NF shows impressive skeletal muscle protection, even when compared to exon-skipping therapy.

**Protection with p-188 NF**

- BL / 10 sal
- *mdx* P188 NF
- *mdx* saline

**Protection with PMO skipper for exon 23**

- *Wild-type*
- *mdx* TA PMO treated
- *mdx* TA untreated

**Notes:** Both studies done in *mdx* mouse hind limb model
- P-188 NF data from Houang et al., 2015 (P-188 NF administered subq, not dose optimized, in vivo)
- PMO data from Sharp et al., 2011 (showing highest dose for exon skipping PMO, administered IM)
Dystrophin, a structural membrane protein, protects the cell membrane from mechanical damage.
No safety signal after 30-145 days in animal studies

Comparison of repeat dosing regimens for P-188 NF
No observed safety signal

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Duration</th>
<th>Maximum Daily Dose (mg/Kg)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>mdx mouse</td>
<td>Phrixus, 2012, subq</td>
<td>30, 100, 100, 250, 1440</td>
<td>*No higher dose tested, NOAEL not established and likely higher. **Male animals less sensitive. † Next higher dose tested 100 mg/Kg</td>
</tr>
<tr>
<td>Sprague-Dawley rat</td>
<td>Magnusson 1986, iv, 30 days</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Sprague-Dawley rat</td>
<td>Duvinage 1996, iv, 1 month</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Beagle dogs</td>
<td>Duvinage 1996, iv, 1 month</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>GRMD dogs</td>
<td>(Metzger 2010, iv) - 60 days</td>
<td>1440</td>
<td></td>
</tr>
<tr>
<td>Monkeys</td>
<td>Duvinage 1996, iv, 1 month</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Dogs</td>
<td>(subq, NDA 21-148*)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Rats†</td>
<td>(subq, NDA 21-148*)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Carmeseal MD™ dose (subq)</td>
<td></td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Notes: All work published in peer-reviewed journals. GRMD dog results are also Metzger verbal communication.
Fluorescein-labeled P-188 NF inserts *in vivo* into *mdx* mouse diaphragm membranes

Fluorescein-labeled P-188 NF (green) overlaying laminin-labeled cell membranes (red) – *In vivo*

- *mdx* mouse dosed with FP-188 NF at 150 mg/kg
- *mdx* mouse dosed with FP-188 NF at 150 mg/kg and P-188 300 mg/kg
- Control mouse dosed with FP-188 NF at 150 mg/kg

Notes: FP – fluorescein-labelled P-188 NF. Animals were treated with fluorescein-labelled P-188 NF and/or P-188 NF at 28 weeks of age – single ip bolus two hours prior to sacrifice. Unpublished Phrixus data
Phrixus scientific and medical advisers

Joseph Metzger  PhD., Inventor and Chair, SMAB. Chair Dept. Physiology, University of Minnesota
Linda Cripe  MD, Pediatric Cardiologist, Nationwide Children’s Hospital Columbus, OH
Steven Goldman  Chief of Cardiology, VA, Tucson, AZ, & Professor of Medicine, Cardiology, University of Arizona
Daniel Kelly  Scientific Director, Burnham Institute, Orlando, FL
Elizabeth McNally  MD/PhD, Professor of Medicine (Cardiology) and Biochemistry and Molecular Genetics, Northwestern University
Hani N. Sabbah  Professor of Medicine, Henry Ford Health Center, Detroit, MI

Jeffrey Towbin  Co-director Heart Institute Le Bonheur Children’s Hospital, chief of Cardiology St. Jude Children’s Research Hospital, chief of Pediatric Cardiology at the University of Tennessee Health Science Center
John Lynn Jefferies  Director, Advanced Heart Failure and Cardiomyopathy, Heart Institute, Cincinnati Children’s, Associate Professor, UC, Department of Pediatrics (Principal Investigator, P-004)
Jonathan Finder  Medical Director, The Children's Home, Professor, Pediatrics, University of Pittsburgh School of Medicine
Thomas Ryan  Principal Investigator, P-004, Director of Clinical Operations, Cardiomyopathy and Heart Failure, Heart Institute, Cincinnati Children’s, Assistant Professor, University of Cincinnati Department of Pediatrics