The Muscle to Move to the Clinic

R&D DAY | OCTOBER 13, 2021, 8 a.m. ET
Forward-Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding Dyne Therapeutics, Inc.’s (the “Company”) strategy, future operations, prospects, plans and objectives of management, the expected timeline for submitting investigational new drug applications, the potential advantages of the Company’s FORCE platform and programs, expectations regarding the translation of preclinical findings to human disease and plans to conduct additional preclinical studies and clinical trials, the anticipated design of clinical trials constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “might,” “objective,” “ongoing,” “plan,” “predict,” “project,” “potential,” “should,” or “would,” or the negative of these terms, or other comparable terminology are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. The Company may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including: uncertainties inherent in the identification and development of product candidates, including the conduct of research activities, the initiation and completion of preclinical studies and clinical trials; uncertainties as to the availability and timing of results from preclinical studies; the timing of and our ability to submit and obtain regulatory approval for investigational new drug applications; whether results from preclinical studies will be predictive of the results of later preclinical studies and clinical trials; the Company’s ability to obtain sufficient cash resources to fund the Company’s foreseeable and unforeseeable operating expenses and capital expenditure requirements; the impact of the COVID-19 pandemic on the Company’s business and operations; as well as the risks and uncertainties identified in Dyne’s filings with the Securities and Exchange Commission (SEC), including the Company’s most recent Form 10-Q and in subsequent filings Dyne may make with the SEC. In addition, the forward-looking statements included in this presentation represent the Company’s views as of the date of this presentation. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company’s views as of any date subsequent to the date of this presentation.

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## Program

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Program

DM1 Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DM1 Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DM1
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Associate Professor of Neurology, University of Milan

Q&A

Closing remarks
Joshua Brumm, President & CEO
Opening remarks
Joshua Brumm, President & CEO

FORCE™ Platform & DMD Program Data
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DMD Program Clinical Development Plan
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Perspectives on DMD
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Q&A
OUR MISSION

Life-transforming therapies
for patients with serious muscle diseases
Dyne – Building the Leading Muscle Disease Company

Proprietary FORCE Platform

• Modern oligo therapeutics for muscle diseases
• Overcoming challenge of muscle delivery
• Plug-and-play therapeutics for multiple targets in skeletal, cardiac and smooth muscle diseases

Rare Muscle Disease Focus

• Robust pipeline: DM1, DMD, and FSHD
• Set standard for evaluating PD in DM1 disease model
• Significant exon skipping & dystrophin expression in DMD
• Significant market opportunities

Delivering for Patients

• Developing multiple first-in-class or best-in-class therapies
• Precision medicine strategy
• Three INDs planned between Q4 2021 - Q4 2022

Exceptional Team

• Deep knowledge of muscle diseases and novel therapeutic modalities
• World-class scientific advisory board
• Supported by leading healthcare investors
### Pipeline Expansion Opportunities

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>TARGET</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>ESTIMATED PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myotonic Dystrophy (DM1)</td>
<td>DMPK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>US: &gt;40,000</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Europe: &gt;74,000</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy (DMD)</td>
<td>Exon 51</td>
<td>DYNE-251</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>US: ~12,000-15,000</td>
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<tr>
<td></td>
<td>Exon 53</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Europe: ~25,000</td>
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<tr>
<td></td>
<td>Exon 45</td>
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<td></td>
<td>Exon 44</td>
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<tr>
<td>Facioscapulohumeral Muscular Dystrophy (FSHD)</td>
<td>DUX4</td>
<td></td>
<td></td>
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<td>US: ~16,000-38,000</td>
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<td></td>
<td></td>
<td></td>
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<td>Europe: ~35,000</td>
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</table>

**Rare Skeletal Cardiac Metabolic**
# Driving To the Clinic with Three INDs Anticipated by YE 2022

<table>
<thead>
<tr>
<th>Disease</th>
<th>DMD</th>
<th>DM1</th>
<th>FSHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro:</strong></td>
<td>Enhanced exon skipping</td>
<td>Enhanced exon skipping</td>
<td>Reduced expression of key DUX4 biomarkers</td>
</tr>
<tr>
<td><strong>In vivo:</strong></td>
<td>Robust, durable exon skipping and dystrophin expression in <em>mdx</em> model</td>
<td><em>DMPK</em> KD, reduction in nuclear foci, splicing correction</td>
<td>Enhanced tissue distribution in NHP</td>
</tr>
<tr>
<td></td>
<td>Transformative exon skipping in NHP cardiac and skeletal muscles</td>
<td>Correction of splicing &amp; reversal of myotonia in HSA LR model</td>
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<tr>
<td></td>
<td>NHP GLP tox results support advancement to the clinic</td>
<td>Robust knockdown of toxic nuclear <em>DMPK</em> in hTfr1/DMSXL model, foci reduction &amp; correction of splicing</td>
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<tr>
<td></td>
<td></td>
<td>Well tolerated in NHP Non-GLP toxicology dose-range finding study</td>
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</tbody>
</table>

**INDs:**
- **DMD:** IND: Q4 2021
- **DM1:** IND: Q1 2022
- **FSHD:** IND: H2 2022
Program

Opening remarks
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Q&A
Dyne FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

ANTIBODY
Proprietary Fab targets TfR1 to enable muscle delivery

LINKER
Clinically validated, enables precise conjugation of multiple payloads to a single Fab

PAYLOAD
Modularity enables rational selection of payload to target the genetic basis of disease

ASO
Nuclear localization

siRNA
Cytoplasmic localization

FORCE Platform Harnesses Cell Biology to Modify Disease

- Harnesses natural mechanism of TfR1 receptor-mediated delivery to transport therapeutics across the cell membrane
- Achieves endosomal escape without any membrane-destabilizing agents
- Distinctive pharmacokinetic profile creates opportunity for durable target engagement and wide therapeutic index
FORCE Platform Designed to Deliver Transformative Therapies

- **Solve the Challenge of Muscle Delivery**
  Leverages TfR1 expression on skeletal, cardiac and smooth muscle

- **Drive Disease Modification**
  Rationally select payloads to target genetic basis of disease

- **Enhance Tolerability**
  Targeted delivery potentially broadens therapeutic window and limits systemic drug exposure

- **Leverage Modularity to Realize Full Potential of FORCE**
  Identified potent siRNA payloads against multiple cardiac and metabolic targets
FORCE Overcame Limitations of ASO Delivery to Muscle in NHP

Note: Results after repeat IV dose of naked ASO or DYNE-251 in male cynomolgus monkeys, 2 x 30 mg/kg on day 0 and day 7, analyzed day 28; n = 4 – 5
DMD: FORCE Achieved Robust Dystrophin Expression Localization to Sarcolemma in Heart

Dystrophin Expression by WB
30 mg/kg 4 Weeks Post-Dose

<table>
<thead>
<tr>
<th>% WT Dystrophin</th>
<th>16</th>
<th>4</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>FORCE-M23D</td>
<td><img src="image1" alt="Dystrophin WB" /></td>
<td><img src="image2" alt="Dystrophin WB" /></td>
<td><img src="image3" alt="Dystrophin WB" /></td>
<td><img src="image4" alt="Dystrophin WB" /></td>
</tr>
</tbody>
</table>

78% of wild-type dystrophin

Dystrophin Localization to Sarcolemma

Vehicle

FORCE-M23D

~80% dystrophin-positive fibers

Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0, analysis on week 4.
DM1: DYNE-101 Reduced Nuclear Foci and Corrected Splicing of Toxic Human DMPK in hTfr1/DMSXL Model

**Toxic Human DMPK RNA KD**

<table>
<thead>
<tr>
<th></th>
<th>PBS</th>
<th>DYNE-101</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs. Vehicle</td>
<td></td>
<td></td>
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<tr>
<td>49% KD</td>
<td>****</td>
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</tbody>
</table>

**Toxic Human DMPK Foci Reduction**

*DMPK Foci, Nuclei, Myofibers*

**Splicing Correction**

*DYNE-101 reduces foci area by 49%*

Note: hTfr1/DMSXL homozygous model. 2 x 10 mg/kg on d0 and d7, analyzed d28.
Composite splicing index includes changes in Ldb3 exon (E) 11, Mbnl2 E6, and Nfix E7. Data are mean ± SD, n = 6 - 7.; * p < 0.05; **** p < 0.0001
FORCE Targeted Delivery to Muscle Tissue Enhanced Potency and Tolerability

**FORCE Offers Potential for Wide Therapeutic Window**

**DM1 mouse model DMSXL**
- 15-30-fold lower dose required for ~60% DMPK KD by FORCE vs naked ASO

**DM1 Non-GLP NHP Toxicology**
- No adverse findings in DRF study in cynomolgus monkeys up to maximal feasible dose

Note: Naked ASO from published data (Pandey et al, 2015) in DMSXL model; Dyne data from hemizygous hTIR1/DMSXL model and WT NHP.
Leveraging Platform Modularity to Realize Full Potential of FORCE, Including siRNA Payloads for Cytoplasmic Targets

Subcellular distribution of ASO and siRNA

FORCE delivers ASO payload for nuclear targets, siRNA payload for cytoplasmic targets

Engineered proprietary siRNA payloads

Identified potent siRNA payloads against multiple cardiac and metabolic targets

Localization graphic adapted from: Ohrt et al: NAR, 2006, v.34, p.1369
Best-in-class Targeted Exon Skipping

Increase dystrophin expression and enable less frequent dosing to potentially stop or reverse disease progression

**OUR APPROACH**

**mdx model**
- Robust, durable exon skipping and dystrophin expression

**NHP**
- Transformative exon skipping in NHP cardiac and skeletal muscles

**Safety**
- NHP GLP tox results support advancement to the clinic

**Current Approved Exon 51 Therapies**
Only increased dystrophin production <1%

Building a Global DMD Franchise of Transformative Therapies
ASO-Mediated Exon Skipping: Mechanism for Disease Correction

Healthy

DMD
Pre-mRNA

DMD
Mature mRNA

Protein

Dystrophin produced

DMD patient \( \Delta \text{ex49-50} \)

Premature stop codon

Out-of-frame

NO functional dystrophin produced

ASO-treated DMD patient \( \Delta \text{ex49-50} \)

Ex 51 ASO

Truncated, functional dystrophin produced

FORCE Dose-Dependently Increased Dystrophin Expression

### Dose-Dependent Increase in Dystrophin Expression

<table>
<thead>
<tr>
<th>Std. Curve (% WT)</th>
<th>64</th>
<th>32</th>
<th>16</th>
<th>4</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg Dystrophin</td>
<td>427 kDa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg/kg Dystrophin</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>30 mg/kg Dystrophin</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Actinin</td>
<td>103 kDa</td>
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</tbody>
</table>

Standard curve - Used pooled WT protein and pooled mdx protein, % indicates amt. of WT spiked into sample.

**Quadriceps**

- Force-M23D: 10, 20, or 30 mg/kg
- Force-M23D IV dose
- Tissue analysis

### Restored Dystrophin Expression

**FORCE Dose (mg/kg)**

- 0
- 10
- 20
- 30
- 40

**% Dystrophin**

- Force-M23D
- Naked ASO

Note: Single IV dose of FORCE-M23D in mdx mouse model on day 0; assessment on day 14.

Single Dose of FORCE Significantly Reduced Serum Creatine Kinase (CK)

CK Levels

- CK is found inside normal muscle and does not leak into serum
- Serum CK is a clinical biomarker of muscle damage
- FORCE significantly reduced serum CK after a single dose

FORCE Demonstrated Functional Benefit with a Single Dose

** P < 0.01
*** P < 0.001
NS: not significant

Distance Traveled in Home Cage Running Wheel
(Assessed 4 weeks after treatment)

Distance Traveled in Open Field Following Hind Limb Fatigue Challenge
(Assessed 2 weeks after treatment)

Note: Single IV 30 mg/kg dose of FORCE-M23D in mdx mouse model. Hind limb fatigue challenge test statistical analysis comparison to wild type (WT) group using one-way ANOVA followed by post-hoc Dunnett’s test.
Study Evaluated Dynamic of FORCE on Dystrophin Expression up to 12 Weeks After a Single Dose

**Endpoints**
- ASO muscle concentration
- Exon skipping by PCR
- Dystrophin protein by WB
- Dystrophin localization by IF

**Tissues analyzed**
- Quadriceps
- Diaphragm
- Heart

PCR, polymerase chain reaction; WB, western blot; IF, immunofluorescence
FORCE Achieved Robust and Durable Skipping and Dystrophin Expression in Cardiac and Skeletal Muscle

Note: Single IV 30 mg/kg dose of FORCE-M23D in mdx mouse model on day 0; N = 3 - 5 per cohort.
FORCE Achieved Robust Dystrophin Expression and Localization to Sarcolemma in Quadriceps at 8 Weeks

Dystrophin Expression by WB
30 mg/kg 8 Weeks Post-Dose

<table>
<thead>
<tr>
<th>% WT Dystrophin</th>
<th>FORCE M23D</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 4 1 0</td>
<td></td>
</tr>
</tbody>
</table>

41% of wild-type dystrophin

Dystrophin Localization to Sarcolemma

Vehicle

FORC-M23D

83% dystrophin-positive fibers

Note: Single IV 30 mg/kg dose of FORCE-M23D in mdx mouse model on day 0, analysis on week 8.
FORCE Achieved Durable Dystrophin Localization to Sarcolemma in Quadriceps

Note: Single IV 30 mg/kg dose of FORCE-M23D in mdx mouse model on day 0, analysis at specified time intervals.
FORCE Achieved Robust Dystrophin Expression and Localization to Sarcolemma in Diaphragm at 4 Weeks

Dystrophin Expression by WB
30 mg/kg 4 Weeks Post-Dose

Note: Single IV 30 mg/kg dose of FORCE-M23D in mdx mouse model on day 0, analysis on week 4.
FORCE Achieved Robust Dystrophin Expression and Localization to Sarcolemma in Heart at 4 Weeks

### Dystrophin Expression by WB
30 mg/kg 4 Weeks Post-Dose

<table>
<thead>
<tr>
<th>% WT Dystrophin</th>
<th>16</th>
<th>4</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
</table>

**FORCE-M23D**

- Dystrophin
- αActinin

78% of wild-type dystrophin

### Dystrophin Localization to Sarcolemma

**Vehicle** vs. **FORCE-M23D**

- Dystrophin
- Laminin

~80% dystrophin-positive fibers

Note: Single IV 30 mg/kg dose of FORCE-M23D in mdx mouse model on day 0, analysis on week 4.
FORCE Achieved Robust and Durable Dystrophin Expression and Sarcolemma Localization in Muscle

### Quadriceps
- **Dystrophin expression by WB**
  - **FORCE M23D**
    - % WT Dystrophin: 16 4 1 0
    - 46% of wild-type dystrophin
  - **α-Actinin**

### Diaphragm
- **Dystrophin expression by WB**
  - **FORCE-M23D**
    - % WT Dystrophin: 16 4 1 0
    - 90% of wild-type dystrophin
  - **α-Actinin**

### Heart
- **Dystrophin expression by WB**
  - **FORCE-M23D**
    - % WT Dystrophin: 16 4 1 0
    - 78% of wild-type dystrophin
  - **α-Actinin**

### Note:
- Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0; analysis on week 4 for all muscles. N= 3 - 5 per cohort.
FORCE Distinctive Pharmacokinetic Profile Delivered Substantial and Durable Dystrophin Expression with a Single Dose

Pharmacokinetics
- Muscle ASO concentration

Pharmacodynamics
- Exon skipping
- Dystrophin restoration

FORCE-M23D 10 mg/kg

FORCE-M23D 30 mg/kg

Note: Single IV dose of FORCE-M23D in mdx mouse model on day 0. N = 3 - 5 per cohort. ASO levels expressed as arbitrary units (AU).
 DYNE-251 Achieved Robust and Dose-Dependent Exon 51 Skipping in DMD Patient Myotubes

Exon 51 Skipping in del52 DMD Myotubes

% Exon 51 Skipping

<table>
<thead>
<tr>
<th>DYNE-251</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
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<tbody>
<tr>
<td></td>
<td>20</td>
<td>40</td>
<td>60</td>
</tr>
</tbody>
</table>

Note: DYNE-251 exposure in DMD patient myotubes for 10 days. N = 3.
Dose Regimen Study in NHPs to Inform Clinical Dose

**Endpoints**
- Exon skipping by PCR

**Tissues analyzed**
- Quadriceps
- Diaphragm
- Heart

**Study Timeline (Weeks)**

<table>
<thead>
<tr>
<th>Study Week</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 x 30 mg/kg</td>
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<tr>
<td>4 x 30 mg/kg</td>
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<tr>
<td>5 x 30 mg/kg</td>
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</table>

- DYNE-251 IV dose
- Tissue analysis
DYNE-251 Achieved Robust Exon Skipping in NHP Skeletal and Cardiac Muscles

Note: Data are means ± SD. N = 3 - 5 per cohort.
DYNE-251 NHP GLP Toxicology Results Demonstrate Favorable Safety Profile That Support Advancement to Clinic

- No dose limiting toxicity observed after five weekly doses up to a maximally feasible dose.
- No changes in cardiac, respiratory, neurologic or ophthalmic endpoints.
- No effect on kidney function.
- No effect on liver function.
- No effect on coagulation.
- NOAEL was identified at the highest dose tested.
DMD Program Summary

Validating Data

**mdx Model**

- **Achieved robust and durable** exon skipping in skeletal and cardiac muscle
- **Dose-dependently increased dystrophin** expression up to 90% of WT based on western blot and ~80% dystrophin-positive fibers
- **Reduced serum CK levels**
- **Demonstrated functional benefit** in multiple standardized assessments

**DYNE-251**

- **Robust and dose-dependent exon skipping** in patient DMD patient myotubes (exon 51)
- **Transformative exon skipping** in NHP cardiac and skeletal muscles
- **Favorable safety profile** in NHP GLP tox study

Potential Advantages

- **Established** clinical and regulatory path
- **Opportunity to accelerate DMD franchise** expansion (exon 53, exon 45, exon 44) to reach additional patient populations

DYNE-251 IND submission planned in Q4 2021
Program

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Q&A
Best-in-class Targeted Exon Skipping

Overview
- Mutation in the DMD gene that encodes for dystrophin
- Onset in first few years of life
- Life expectancy ~30 years

Clinical Presentation
- Muscle weakness
- Progressive loss of function
- Loss of ambulation
- Respiratory/cardiac failure

Population
- ~12,000 - 15,000 (US)
- ~25,000 (Europe)

OUR APPROACH

Increase dystrophin expression and enable less frequent dosing to potentially stop or reverse disease progression

Current Approved Exon 51 Therapies
- Only increased dystrophin production <1%
Global, Multi-disciplinary KOL Input

- ✔ Overall design for the MAD study in patients with DMD amenable to exon 51 skipping
- ✔ Patient population, biomarker and functional endpoints, and key safety considerations
- ✔ Natural history data to contextualize clinical trial data for patients and families, clinicians, payers, regulators

Global Advocacy Leaders, Patient and Caregiver Input

- ✔ Considerations for trial selection
- ✔ Clinical trial protocol and visit schedule
- ✔ Minimizing patient burden during trial conduct
- ✔ Ensuring support and education to patients and families

KOL input includes U.S. and European thought leaders across: pediatric & adult neurology; physical medicine and rehabilitation; cardiology, physical therapy. Advocacy leaders, patient and caregiver input includes U.S. and European advocacy leaders, young men with DMD, caregivers for individuals living with DMD.
The endpoint I’m looking for is to halt the progression of the disease. I don’t want to lose any more function.

We would love to have someone recognize that stability for this community is something we would love to achieve. Yes, we would love a cure for our boys, but sometimes just stopping progression would be great.

Time is not on our side… We just feel a huge sense of urgency to get the best set of treatments…
Proposed Clinical Trial to Evaluate DYNE-251 in Patients with DMD

**MULTIPLE ASCENDING DOSE (MAD)**

**Design**
- Multiple Ascending Dose
- Placebo Controlled
- Global
- LTE

**Population**
- Patients with symptomatic DMD and mutation amenable to exon 51 skipping therapy
- Ages 4 to 16 years
- ~30-40 male participants
- Ambulant and non-ambulant

**LONG-TERM EXTENSION (LTE)**

**Endpoints***
- Safety and tolerability
- PK/PD
- Dystrophin by Western Blot
- Measures of muscle function
  - Upper and lower limbs
  - Respiratory

Planned IND Submission in Q4 2021

* Proposed endpoints include primary, secondary and exploratory
Dyne Committed to Developing Global DMD Franchise

Approximately 80% of patients have genotypes amenable to exon skipping.

- Exon 51 – 13%
- Exon 53 – 8%
- Exon 45 – 8%
- Exon 44 – 6%
- Exon 50 – 4%
- Exon 52 – 4%
- Exon 43 – 4%
- Exon 55 – 2%
- Exon 8 – 2%
- Other exon skips – ~30%
- May not be amenable to exon skipping – ~20%
Program

Opening remarks
Joshua Brumm, President & CEO

FORCE™ Platform & DMD Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DMD Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DMD
John Day, M.D., Ph.D., Professor of Neurology and Pediatrics, and Director of the Neuromuscular Division, Stanford Neuroscience Health Center

Q&A
Duchenne Muscular Dystrophy: Current Unmet Needs & Emerging Therapies

John W. Day, MD, PhD

Professor, Departments of Neurology and Pediatrics
Director, Division of Neuromuscular Medicine
Stanford University School of Medicine
Disclosures

In addition to funding from NIH/NINDS, MDA, CureSMA, SMA Foundation and the Myotonic Dystrophy Foundation, in the past 12 months I have had the following financial relationships with the manufacturers of commercial products or providers of commercial services at least indirectly related to this presentation:

- Research grants support – AMO, Astellas Gene Therapies, Avidity, Biogen, Cytokinetics, Ionis, Novartis Gene Therapies, Sanofi/Genzyme, Roche, Sarepta, Scholar Rock

- Consultant or Advisor – Affinia, AMO, Avidity, Biogen, Cytokinetics, Novartis, Novartis Gene Therapies, PepGen, Roche, Sarepta
Dystrophinopathies: Clinical categorization

- **DMD:**
  - Symptom onset age > 2 years
  - CK 50-100X normal
  - Lower limb and pelvic girdle weakness
  - Loss of ambulation by early teens
  - Cardiopulmonary complications leading to death
- **1:3500 to 5000 live male births**
- **>12,000 boys registered in MDA clinics**

- **BMD:**
  - Classic: loss of ambulation > age 12
  - Alternatively
    - “intermediate” MD LOA 12 - 15y
    - BMD LOA > age 15y
  - Adult LGMD
  - Myalgias
  - Isolated Cardiomyopathy
Role of Dystrophin in Muscle Function

Fairclough RJ, et al. 2013
Duchenne vs Becker

<table>
<thead>
<tr>
<th>Type of Dystrophinopathy</th>
<th>Clinical Features</th>
<th>Biopsy Findings</th>
<th>Genetic Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne</td>
<td>LOA ≤12y</td>
<td>No Dystrophin</td>
<td>Null</td>
</tr>
<tr>
<td>Becker</td>
<td>LOA ≥15y</td>
<td>Reduced or Abnormal Dystrophin</td>
<td>In Frame</td>
</tr>
</tbody>
</table>

- Size of deletion does not correlate well with phenotype
- Out-of-frame deletions are DMD ~90% of the time
- In-frame deletions are more likely to result in translation of a protein with partial function
## Dystrophin Genotype – Phenotype

<table>
<thead>
<tr>
<th>MUTATION CLASS</th>
<th>DMD</th>
<th>IMD</th>
<th>BMD</th>
<th>Unknown (B/DMD)</th>
<th>Manifesting Carrier&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Carrier (all phenotyp)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DELETION</td>
<td>283</td>
<td>15</td>
<td>55</td>
<td>107</td>
<td>3</td>
<td>14</td>
<td>477</td>
<td>42.9%</td>
</tr>
<tr>
<td>in</td>
<td>30</td>
<td>2</td>
<td>36</td>
<td>17</td>
<td>1</td>
<td>2</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>out</td>
<td>243</td>
<td>13</td>
<td>18</td>
<td>88</td>
<td>1</td>
<td>12</td>
<td>375</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>STOP</td>
<td>176</td>
<td>4</td>
<td>30</td>
<td>46</td>
<td>4</td>
<td>34</td>
<td>294</td>
<td>26.5%</td>
</tr>
<tr>
<td>UGA</td>
<td>60</td>
<td>1</td>
<td>13</td>
<td>20</td>
<td>3</td>
<td>15</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td>UAG</td>
<td>71</td>
<td>0</td>
<td>11</td>
<td>13</td>
<td>0</td>
<td>4</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>UAA</td>
<td>45</td>
<td>3</td>
<td>6</td>
<td>13</td>
<td>1</td>
<td>15</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>SUBEXONIC</td>
<td>70</td>
<td>0</td>
<td>10</td>
<td>32</td>
<td>1</td>
<td>14</td>
<td>127</td>
<td>11.4%</td>
</tr>
<tr>
<td>FS Ins</td>
<td>22</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>FS Del</td>
<td>46</td>
<td>0</td>
<td>4</td>
<td>23</td>
<td>0</td>
<td>8</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>FS Ins/Del</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>in-frame deletion</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUPLICATION</td>
<td>87</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>5</td>
<td>5</td>
<td>122</td>
<td>11.0%</td>
</tr>
<tr>
<td>SPLICE</td>
<td>22</td>
<td>3</td>
<td>7</td>
<td>18</td>
<td>2</td>
<td>12</td>
<td>64</td>
<td>5.8%</td>
</tr>
<tr>
<td>MISSENSE</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>1.4%</td>
</tr>
<tr>
<td>PSEUDOEXON</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>0.5%</td>
</tr>
<tr>
<td>POTENTIAL</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>0.5%</td>
</tr>
<tr>
<td>OTHER</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>TOTAL MUTATIONS</td>
<td>642</td>
<td>32</td>
<td>120</td>
<td>220</td>
<td>15</td>
<td>82</td>
<td>1111</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Flanigan, et al., *Hum Mutation*, 2009
Exon skippable deletions ~80% of Duchenne

Distribution of mutations in an unselected cohort
(Dent et al; AJMG, 2005)

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>DMD</th>
<th>BMD</th>
<th>Carrier</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 exon deletion</td>
<td>32</td>
<td>13</td>
<td></td>
<td>45 (66%)</td>
</tr>
<tr>
<td>Premature Stop</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>9 (13%)</td>
</tr>
<tr>
<td>Missense</td>
<td>1</td>
<td>2</td>
<td></td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Frameshift insertion or deletion</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>≥1 exon duplication</td>
<td>3</td>
<td>1</td>
<td></td>
<td>4 (6%)</td>
</tr>
<tr>
<td>No mutation detected</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>21</td>
<td>2</td>
<td>68</td>
</tr>
</tbody>
</table>

Currentl available methodology can detect 93%-96% of dystrophinopathy mutations from blood samples
(Yan et al, Hum Mutat 2004)

https://www.cureduchenne.org/cure/exon-skipping/
Emerging Therapies

- Exon skipping
- Gene replacement
- CRISPR/Cas9 gene editing
Eteplirsen for treatment of 51 skip-amenable patients with DMD
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Baseline % normal dystrophin</th>
<th>Week 48 % normal dystrophin</th>
<th>Change from Baseline % normal dystrophin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.13</td>
<td>0.26</td>
<td>0.13</td>
</tr>
<tr>
<td>2</td>
<td>0.35</td>
<td>0.36</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.06</td>
<td>0.37</td>
<td>0.31</td>
</tr>
<tr>
<td>4</td>
<td>0.04</td>
<td>0.10</td>
<td>0.06</td>
</tr>
<tr>
<td>5</td>
<td>0.17</td>
<td>1.02</td>
<td>0.85</td>
</tr>
<tr>
<td>6</td>
<td>0.37</td>
<td>0.30</td>
<td>-0.07</td>
</tr>
<tr>
<td>7</td>
<td>0.17</td>
<td>0.42</td>
<td>0.25</td>
</tr>
<tr>
<td>8</td>
<td>0.24</td>
<td>1.57</td>
<td>1.33</td>
</tr>
<tr>
<td>9</td>
<td>0.11</td>
<td>0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>10</td>
<td>0.05</td>
<td>0.47</td>
<td>0.43</td>
</tr>
<tr>
<td>11</td>
<td>0.02</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td>12</td>
<td>0.18</td>
<td>0.21</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>0.16</strong></td>
<td><strong>0.44</strong></td>
<td><strong>0.28; p=0.008</strong></td>
</tr>
</tbody>
</table>
FDA Approved Exon Skipping for DMD

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Mechanism of Action</th>
<th>Chemistry</th>
<th>Route of Administration</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>eteplirsen</td>
<td>exon 51 skipping</td>
<td>PMO</td>
<td>intravenous</td>
<td>weekly</td>
</tr>
<tr>
<td>golodirsen</td>
<td>exon 53 skipping</td>
<td>PMO</td>
<td>intravenous</td>
<td>weekly</td>
</tr>
<tr>
<td>viltolarsen</td>
<td>exon 53 skipping</td>
<td>PMO</td>
<td>intravenous</td>
<td>weekly</td>
</tr>
<tr>
<td>casimersen</td>
<td>exon 45 skipping</td>
<td>PMO</td>
<td>intravenous</td>
<td>weekly</td>
</tr>
</tbody>
</table>
Predicting clinical benefit of therapies

- There is no human correlate to the engineered microdystrophin proteins in trial
- In contrast, exon skipping results in isoforms identical to native BMD-associated isoforms, allowing researchers to predict maximal benefit

Findlay et al, Annals Neurol (2015); 77:668-674

*Graph showing*:

DMD exon 45 skip-equivalent genotypes vs age at last ambulation

- Genotype: △45-46, △45-47, △45-48
- Phenotype: 4/4 DMD, 17/17 BMD, 19/20 BMD, 1/20 IMD

- NON-AMBULANT
- AMBULANT
- IMD
Clinical Effects of Dystrophin Expression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>42</td>
<td>34</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Dystrophin protein quantity, %</td>
<td>0</td>
<td>&gt;0 and &lt;5</td>
<td>≥5</td>
<td></td>
</tr>
<tr>
<td>Canonical splice sites mutations, n (%)</td>
<td>17 (40)</td>
<td>12 (35)</td>
<td>8 (57)</td>
<td>0.374</td>
</tr>
<tr>
<td>Pseudoexon and noncanonical splice site mutations, n (%)</td>
<td>7 (17)</td>
<td>16 (47)</td>
<td>4 (29)</td>
<td>0.009</td>
</tr>
<tr>
<td>Nonsense mutations in “in-frame” exon, n (%)</td>
<td>18 (43)</td>
<td>6 (18)</td>
<td>2 (14)</td>
<td>0.023</td>
</tr>
<tr>
<td>DMD [LoA at &lt;13 yr of age], n (%)</td>
<td>31 (74)</td>
<td>6 (18)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IMD [LoA at ≥13 and &lt;16 yr of age], n (%)</td>
<td>4 (10)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0.283</td>
</tr>
<tr>
<td>BMD [LoA at ≥16 yr of age], n (%)</td>
<td>1 (2)</td>
<td>21 (61)</td>
<td>8 (57)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Clinical Effects of Dystrophin Expression

Number at risk:
A: 41 41 37 29 16 10 2
B: 34 34 31 27 18 16 14
C: 14 14 14 12 8 8 8

Median age at event (years):
A: 28.7
B: Undefined
C: Undefined

Hazard Ratio (group B/A):  
HR = 0.16 (95% CI: 0.07 to 0.48)
AAV Gene Therapy for DMD

A AAVrh74 — MHCK7 Promoter — N-term — R1 — R2 — R3 — R4 — CR — Nationwide/Sarepta

B AAV9 — CK8 Promoter — N-term — R1 — R16 — R17 — R23 — R24 — CR — SGT-001


Shieh P., Neurotherapeutics (2018)
Unknovns about AAV Gene Replacement

– How to treat subjects with AAV antibodies
– How to retreat all subjects
– Trans-gene reaction if part of micro-dys protein is novel
– Risks of high AAV viral load
– Distribution: muscle; muscle fiber; myonuclei
– Duration: Dividing cells; Non-dividing cells
– Transduction of satellite/progenitor cells
Hope for patients

- Next-generation technologies may allow for
  - Durable and titratable therapies, with much less frequent dosing than current treatments, for all stages of disease
  - Treating cardiac and pulmonary issues which lead to significant morbidity and mortality
  - Potential to significantly slow or even stop progression
- Goal is to extend patients lives and quality of life
Program

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Perspectives on DMD
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Q&A
Program

DM1 Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DM1 Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DM1
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Associate Professor of Neurology, University of Milan

Q&A

Closing remarks
Joshua Brumm, President & CEO
Developing Transformative Therapies for People Living with DM1

DM1 Patient Cells
- DMPK KD, reduction in nuclear foci, splicing correction

In Vivo Disease Models
- Correction of splicing & reversal of myotonia in HSA^{LR} model
- Robust KD of toxic nuclear DMPK in hTfR1/DMSXL model, foci reduction & correction of splicing

Safety
- Well tolerated in NHP Non-GLP toxicology dose-range finding study

OUR APPROACH

Disease-Modifying Nuclear DMPK Knockdown

Targeting toxic gain of function DMPK RNA to potentially stop or reverse disease progression

NO approved therapies
FORCE Targets the Genetic Basis of DM1 to Correct Splicing

DNA Triplet Repeats

Toxic RNA Forms Foci

RNA Binds Splicing Proteins

Clinical Presentation

- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

FORCE designed to address the genetic basis of disease by targeting toxic nuclear DMPK RNA to correct spliceopathy
An illustration and accompanying text explaining the mechanism of DMPK RNA targeting by FORCE (FORCE Targets Toxic Nuclear DMPK RNA). The text describes how FORCE binds to toxic DMPK mRNA, leading to the recruitment of ASO (antisense oligonucleotide) and RNaseH1. RNaseH1 cleaves the DMPK RNA, releasing MBNL (Muscleblind-like 1) protein to restore splicing in the nucleus. The toxic DMPK mRNA is unable to leave the nucleus, while normal DMPK mRNA is able to do so.
Data from Multiple DM1 Models Demonstrate that FORCE Delivers to Muscle and Drives Disease Modification
In Vitro Models Represent DM1 Patient Population With Wide Range of CTG Repeats

DYNE-101 Demonstrated Robust Dose-dependent \textit{DMPK} KD, Foci Reduction, and Splicing Correction

380 CTG Repeats DM1 Myotubes

\textbf{DMPK} mRNA KD by qPCR

\textbf{DMPK} foci reduction by FISH

\textbf{BIN1} mis-splicing correction by qPCR

2,600 CTG Repeats DM1 Myotubes

\textbf{DMPK} mRNA KD by qPCR

\textbf{DMPK} foci reduction by FISH

\textbf{BIN1} mis-splicing correction by qPCR

Note: Data are mean ± SD, \(n=4\). Foci reduction based on foci area corrected for nuclear area.
In Vivo Models Represent DM1 Patient Population With Wide Range of CTG Repeats

FORCE Dose-Dependently Corrected Splicing and Reversed Myotonia in the HSA\textsuperscript{LR} DM1 Mouse Model

**Splicing Correction in Multiple Muscles**

- **Quadriiceps**
- **Gastrocnemius**
- **Tibialis Anterior**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Splicing Derangement</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT splicing</td>
<td>0.00</td>
</tr>
<tr>
<td>Saline</td>
<td>0.75</td>
</tr>
<tr>
<td>FORCE 10mg/kg</td>
<td>0.25</td>
</tr>
<tr>
<td>FORCE 20mg/kg</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Myotonia Grade (EMG)**

- 0.0: no myotonia
- 1.0: occasional myotonic discharge in less than 50% of needle insertions
- 2.0: myotonic discharge in greater than 50% of needle insertions
- 3.0: myotonic discharge with nearly every insertion

**Near Complete Myotonia Reversal Within 14 Days After a Single Low Dose**

Note: HSA\textsuperscript{LR} mice, single dose 14-day study. Overall splicing derangement indexed to WT level of 0.00. EMG myotonic discharges were graded by a blinded examiner on a 4-point scale: 0, no myotonia; 1, occasional myotonic discharge in less than 50% of needle insertions; 2, myotonic discharge in greater than 50% of needle insertions; 3, myotonic discharge with nearly every insertion.
FORCE Dose-Dependently Corrected Splicing in Multiple RNAs in HSA\textsuperscript{LR} DM1 Mouse Model After a Single Dose

Gastrocnemius

Overall Splicing Derangement

WT Splicing; Splicing Derangement = 0.0
FORCE Dose-Dependently Corrected Splicing and Reversed Myotonia in the HSA^{LR} DM1 Mouse Model

Splicing Correction in Multiple Muscles

Near Complete Myotonia Reversal Within 14 Days After a Single Low Dose

Note: HSA^{LR} mice, single dose 14-day study. Overall splicing derangement indexed to WT level of 0.00. EMG myotonic discharges were graded by a blinded examiner on a 4-point scale: 0, no myotonia; 1, occasional myotonic discharge in less than 50% of needle insertions; 2, myotonic discharge in greater than 50% of needle insertions; 3, myotonic discharge with nearly every insertion.
hTfR1/DMSXL: Innovative Model Developed by Dyne to Evaluate PD By Measuring Toxic Human Nuclear DMPK KD

- Expresses human TfR1 receptor, enabling use of human TfR1-targeting Fabs
- Underestimates potency, expressing >10 times less human toxic DMPK vs. mouse DMPK

Note: DMSXL mice first described in PLOS Genetics 2012, 8(11):e1003043
Toxic Human $DMPK$ is Trapped in Nuclei in hTfR1/DMSXL Model

Note: fractions from gastrocnemius of vehicle-treated hTfR1/DMSXL hemizygous model. Data are mean ± SD; n=2
DYNE-101 Achieved Robust Toxic Human DMPK KD in Nuclei of hTfR1/DMSXL Model

Note: hTfR1/DMSXL hemizygous model. Single IV 10 mg/kg dose on d0, samples from gastrocnemius analyzed d28; Data are mean ± SD; n = 2
DYNE-101 Demonstrated Robust Toxic Human DMPK KD in hTfR1/DMSXL Model

Note: hTfR1/DMSXL hemizygous model. 2 x 10 mg/kg, d0 and d7, analyzed d14; Data are mean ±SD; **p < 0.01, ***p < 0.001, ****p < 0.0001, significant by ANOVA; n=6-9
hTfR1/DMSXL Homozygous Model Enables Assessment of Splicing Correction with DYNE-101

Toxic nuclear human DMPK

hTfR1/DMSXL hemizygous
- One copy of the toxic human DMPK gene
- No splicing phenotype

hTfR1/DMSXL homozygous
- Two copies of the toxic human DMPK gene
- DM1 splicing phenotype
DYNE-101 Demonstrated Toxic \textit{DMPK} KD and Splicing Correction in Muscle of hTfR1/DMSXL Homozygous Model

**Toxic Human \textit{DMPK} KD**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>hTfR1/DMSXL - PBS</th>
<th>hTfR1/DMSXL – DYNE-101</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diaphragm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMPK vs. PBS</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Tibialis Anterior</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMPK vs. Vehicle</td>
<td><strong>44% KD</strong></td>
<td><strong>49% KD</strong></td>
</tr>
<tr>
<td><strong>Gastrocnemius</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMPK vs. Vehicle</td>
<td></td>
<td><strong>44% KD</strong></td>
</tr>
</tbody>
</table>

**Splicing correction**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>hTfR1 - PBS</th>
<th>hTfR1/DMSXL - PBS</th>
<th>hTfR1/DMSXL – DYNE-101</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diaphragm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite splicing index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tibialis Anterior</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite splicing index</td>
<td></td>
<td></td>
<td>********</td>
</tr>
<tr>
<td><strong>Gastrocnemius</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite splicing index</td>
<td></td>
<td></td>
<td>********</td>
</tr>
</tbody>
</table>

Note: hTfR1/DMSXL homozygous model. 2 x 10 mg/kg on d0 and d7, analyzed d28. Composite splicing indices include Bin1 E11, Insr E11, Ldb3 E11, Mbnl2 E6, Nfix E7, and Ttn E313 mis-splicing measured by qRT-PCR. Data are means ± SD; n = 4–7; **** p < 0.0001 by t-test.
DYNE-101 Demonstrated Toxic DMPK KD, Foci Reduction and Splicing Correction in Heart of hTfR1/DMSXL Homozygous Model

**Toxic Human DMPK RNA KD**

<table>
<thead>
<tr>
<th>PBS</th>
<th>DYNE-101</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>0.6 ** ****</td>
</tr>
<tr>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>0.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**DMPK vs. Vehicle**

- 49% KD

**Toxic Human DMPK Foci Reduction**

- DYNE-101 reduces foci area by 49%*

**Splicing Correction**

- hTfR1 - PBS
- hTfR1/DMSXL - PBS
- hTfR1/DMSXL – DYNE-101

---

Note: hTfR1/DMSXL homozygous model. 2 x 10 mg/kg on d0 and d7, analyzed d28. Composite splicing index includes changes in Ldb3 exon (E) 11, Mbnl2 E6, and Nfix E7. Data are mean ± SD, n = 6 - 7.; * p <0.05; **** p < 0.0001
hTfR1/DMSXL Mice are a PK/PD Model and Non-Human Primates are a PK and Tolerability Model

- **Uptakes human TfR1 targeting Fabs**
  - hTfR1
  - hTfR1/DMSXL

- **Expresses human toxic DMPK**
  - DMSXL

**Cytoplasmic normal DMPK**
- Asian cynomolgus monkey

**Enables measurement of human toxic nuclear DMPK KD**
- 5' Human DMPK mRNA
- 3' (CUG) ~1,000

**Allows measurement of normal cytoplasmic DMPK KD**
- 5' Cynomolgus DMPK mRNA
- 3'
FORCE Achieved Enhanced Distribution and WT DMPK KD Across NHP Skeletal, Cardiac and Smooth Muscles

Note: WT NHP with WT DMPK expression, n=3 per group, single dose IV at 10mg per kg for ASO, 14-day study.
DYNE-101 Well Tolerated in NHP Non-GLP Toxicology Dose-Range Finding Study

- No adverse findings in cynomolgus monkeys after repeat ascending doses of DYNE-101
- No effects on body weight with no clinical signs of toxicity
- No test article-related macroscopic observations or organ weight changes
- No effect on kidney and liver function
DM1 Program Summary

Validating Data

- **Targeted** toxic *DMPK* in the nucleus in patient cells
- **Robust and durable toxic human DMPK KD** in novel hTfR1/DMSXL model
- **Reduced nuclear foci** *in vitro & in vivo*
- **Corrected splicing** changes *in vitro & in vivo*
- **Reversed myotonia** in HSA\textsuperscript{LR} model
- **Delivered** *DMPK* targeting ASO to mouse and NHP muscle tissues
- **Favorable safety profile** in NHP DRF study

Potential Advantages

- **Tractable development** with rapid path to human PoC
- **Efficient** commercial model, addressable with focused sales force

DYNE-101 IND submission planned in Q1 2022
<table>
<thead>
<tr>
<th>Program</th>
</tr>
</thead>
</table>
| **DM1 Program Data**  
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer |
| **DM1 Program Clinical Development Plan**  
Wildon Farwell, M.D., MPH, Chief Medical Officer |
| Perspectives on DM1  
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Associate Professor of Neurology, University of Milan |
| **Q&A** |
| **Closing remarks**  
Joshua Brumm, President & CEO |
Developing Transformative Therapies for People Living with DM1

Overview
- Mutation in the DMPK gene
- Onset at any point, depending on DM1 phenotype
- Life expectancy of 45 - 60 years

Clinical Presentation
- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

Population
- >40,000 (US)
- >74,000 (Europe)

OUR APPROACH
Disease-Modifying Nuclear DMPK Knockdown
Targeting toxic gain of function DMPK RNA to potentially stop or reverse disease progression

NO approved therapies
DM1 Clinical Development Plan Informed by KOL and Patient Community Input

**Global, Multi-disciplinary KOL Input**

- Overall design for the MAD study in patients over 18 yrs
- Splicing, myotonia, measures of strength & function, key safety considerations
- Natural history data to contextualize clinical trial data for patients and families, clinicians, payers, regulators

**Global Advocacy Leaders, Patient and Caregiver Input**

- Considerations for trial selection
- Clinical trial protocol and visit schedule
- Minimizing patient burden during trial conduct
- Ensuring support and education to patients and families

KOL input includes U.S. and European thought leaders across: pediatric & adult neurology; physical medicine and rehabilitation; cardiology, physical therapy. Advocacy leaders, patient and caregiver input includes U.S. and European advocacy leaders, young men with DMD, caregivers for individuals living with DMD.
DM1 Clinical Development Plan Informed by Natural History Study

**END-DM1 Natural History Study**

- 700 adults (age 18-70 years); 2-year follow-up
- Informs biomarker testing methods and endpoint selection for clinical trials
- Access to study data and biological samples

Sponsored by:

Supporters of END-DM1 include Dyne and:

- Myotonic Dystrophy Clinical Research Network (DMCRN)
- MDA
- FDA
- Myotonic Dystrophy Foundation
DM1 Community Urgently Needs Treatment Options

“Being so dependent on others for such simple tasks... is extremely frustrating and demoralizing.”

“I used to love to dance. I lost so many things I used to love to do.”

“Each and every day brings a new challenge for all our children, and those challenges will certainly increase as the disease progresses.”
Proposed Clinical Trial to Evaluate DYNE-101 in Patients with DM1

**Design**
- Multiple Ascending Dose
- Placebo Controlled
- Global
- LTE

**Population**
- Patients with symptomatic DM1
- Ages 18+
- ~40-50 participants

**Endpoints**
- Safety and tolerability
- PK/PD
- Splicing Index
- Measures of muscle strength and function
  - Myotonia
  - Ambulation
  - Respiratory

Planned IND Submission in Q1 2022

* Proposed endpoints include primary, secondary and exploratory
Committed to Addressing Full Spectrum of DM1 Population

Program

DM1 Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

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Q&A

Closing remarks
Joshua Brumm, President & CEO
FROM BENCH TO BED IN MYOTONIC DYSTROPHY

WHERE ARE WE?

Valeria Sansone, MD, PhD
Professor of Neurology, University of Milan
Clinical and Scientific Director of the NEMO Center
DM1: An RNA-mediated Disorder

expands CUG repeat (RNA)

expanded CTG repeat (DNA)

DM1 is a spliceopathy

faulty regulation of alternative splicing

RNA inclusions

myotonia

loss of CLC-1 chloride channel
Aberrant Splicing ➔ Signs & Symptoms

**Skeletal muscle**
- Myotonia:
- Muscle weakness (myopathy):
- Muscle wasting (atrophy):
- Respiratory failure:
- Myalgia:
- Conduction defect/block:
- White/gray matter changes:
- Excessive daytime sleepiness:
- Fatigue:
- Cognitive decline:
- Behavioral changes:

<table>
<thead>
<tr>
<th>Aberrant Splicing</th>
<th>Signs &amp; Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLCN1 e7A</strong></td>
<td>Difficulty swallowing: unknown</td>
</tr>
<tr>
<td><strong>CACNA1S e29, BIN1 e11,</strong></td>
<td>Constipation, diarrhea: unknown</td>
</tr>
<tr>
<td><strong>DMD e78, RYR1 e70</strong></td>
<td>Bloating: unknown</td>
</tr>
<tr>
<td><strong>PKM e10, DMD e78</strong></td>
<td>unknown</td>
</tr>
<tr>
<td><strong>SCN5A e6, TNNT2 e5,</strong></td>
<td>unknown</td>
</tr>
<tr>
<td><strong>miR-1</strong></td>
<td>Cataracts: unknown</td>
</tr>
</tbody>
</table>

**Cardiac muscle**
- Conduction defect/block:
- White/gray matter changes:
- Excessive daytime sleepiness:
- Fatigue:
- Cognitive decline:
- Behavioral changes:

**Gastrointestinal**
- Difficulty swallowing: unknown
- Constipation, diarrhea: unknown
- Bloating: unknown

**Sensory**
- Cataracts: unknown
- Ptosis: unknown
- Hearing impairment: unknown

**Endocrine**
- Insulin resistance: unknown
- Hypogonadism: unknown
- Hyperparathyroidism: unknown
- Frontal balding: unknown

**Immune**
- Autoimmune diseases: unknown
- Cancer: unknown
DM1: Onset At All Ages

- **CONGENITAL FORM**
  - Birth
- **PEDIATRIC ONSET**
  - 30 days
- **ADULT ONSET**
  - 18 yrs
- **LATE ONSET**
  - 40 yrs
Burden Of Disease

Distal muscle weakness

Cardiac arrhythmias

Smooth muscle involvement

Stumbles and falls

Swallowing difficulties
GI symptoms

Early PM/ICD implantation
DYNE-101 demonstrated Robust Toxic Human DMPK KD in hTfR1/DMSXL Model

ASGCT 2021; hTfR1/DMSXL hemizygous model. 2 x 10 mg/kg, d0 and d7, analyzed d14; Data are mean ± SD; **p < 0.01, ***p < 0.001, ****p < 0.0001, significant by ANOVA; n=6-9
Burden Of Disease

Respiratory muscle weakness

Cognitive & behavioral abnormalities

Secretion management
Daytime hypoxia
Hypercapnia

Central fatigue, apathy,
frontal dysexecutive syndrome,
Excessive Daytime Sleepiness
Unmet Needs

NO TREATMENTS SO FAR

Transcriptional silencing
1. Inhibition of RNA polymerase co-factors
2. Small molecules that bind to GC-rich repeats

Post-transcriptional silencing
3. Antisense oligonucleotides
4. Small RNAs targeting CUG repeats

Inhibiting interactions between MBNL and toxic RNA
5. Small molecules - monomers and polymers
6. Peptides

Targeting pathways downstream of RNA toxicity

Thornton C et al. Curr Opin Genetics 2017

FORCE Platform

THE DM-CRN: END-DM1 STUDY:
- Which patients?
- Which outcomes?
Unmet needs: No Treatment

FORCE Platform

- Durable knockdown of toxic human nuclear DMPK RNA in the hTfR1/DMSXL model
- Correction of splicing in the hTfR1/DMSXL model (advantage of the model is to quantify splice products)
- Robust targeted effects on skeletal, diaphragm, cardiac, smooth muscles in preclinical studies
Unmet Needs: Which Patients? Which Outcomes?

Myotonic Dystrophy – Clinical Research Network (DM-CRN)

- 700 Patients
- Multicenter
- International (US & EU) Sites
- Trained staff
- Harmonization of protocols and procedures

October 18th, 2019
Conclusions

WHY IS THIS WORK IMPORTANT?

- DM is the most frequent muscular dystrophy (1:2500 adults)
- Very variable: very severe neonatal form to late onset forms
- Multiple organ involvement
- Very high patient and family burden, social impact, productivity

HOW CAN WE IMPACT ON THIS DISEASE

- Trial readiness
- Target the main domains of impact/disease burden
- Provide access to as many patients as possible worldwide
«What phenomena do clinicians observe that are crying for the attention of laboratory researchers?»

«...need to take the clinical question from the bed to the bench....carrying the answer from the bench back to the bed, and then extending the benefits to the field—to the wider world»
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Joshua Brumm, President & CEO
The Muscle to Move to the Clinic

**DMD**
- **In vitro:**
  - Enhanced exon skipping
- **In vivo:**
  - Robust, durable exon skipping and dystrophin expression in *mdx* model
  - Transformative exon skipping in NHP cardiac and skeletal muscles
  - NHP GLP tox results support advancement to the clinic

**DM1**
- **In vitro:**
  - *DMPK* KD, reduction in nuclear foci, splicing correction
- **In vivo:**
  - Correction of splicing & reversal of myotonia in HSA^LR^ model
  - Robust knockdown of toxic nuclear *DMPK* in hTfr1/DMSXL model, foci reduction & correction of splicing
  - Well tolerated in NHP Non-GLP toxicology dose-range finding study

**FSHD**
- **In vitro:**
  - Reduced expression of key DUX4 biomarkers
- **In vivo:**
  - Enhanced tissue distribution in NHP

**IND**
- **DMD:** Q4 2021
- **DM1:** Q1 2022
- **FSHD:** H2 2022
Targeting the genetic basis of serious muscle diseases to
STOP OR REVERSE DISEASE PROGRESSION

FORCE
PLATFORM

Robust
PIPELINE

Delivering
FOR PATIENTS

Exceptional
TEAM

Three INDs planned between Q4 2021 - Q4 2022