Building the World's Leading Muscle Disease Company

Jordan, *living with DMD*

SPOTLIGHT ON THE CLINIC VIRTUAL EVENT | SEPT.12, 2022, 7:30-9 am 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's strategy, future operations, prospects and plans, objectives of management, the potential of the FORCE platform, and the trial design, anticipated timelines for dosing patients, and the planned timeline for reporting data for the DYNE-251 and DYNE-101 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. Dyne 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 initiation and completion of preclinical studies and clinical trials; uncertainties as to the availability and timing of results from preclinical studies and clinical trials; the timing of and Dyne's ability to initiate and enroll patients in clinical trials; whether results from preclinical studies will be predictive of the results of later preclinical studies and clinical trials; whether Dyne's cash resources will be sufficient to fund the Company's foreseeable and unforeseeable operating expenses and capital expenditure requirements; uncertainties associated with the impact of the COVID-19 pandemic on Dyne'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 Dyne's views as of the date of this presentation. Dyne anticipates that subsequent events and developments will cause its views to change. However, while Dyne 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 Dyne's views as of any date subsequent to the date of this presentation.

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Program

Opening remarks
Joshua Brumm, President & CEO

DYNE-101 ACHIEVE Trial
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on Myotonic Dystrophy Type 1 (DM1)
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Professor of Neurology, University of Milan

Q&A

Program

DYNE-251 DELIVER Trial
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on Duchenne Muscular Dystrophy (DMD)
Richard Finkel, M.D., Director, Center for Experimental Neurotherapeutics, St. Jude Children's Research Hospital

Q&A

Closing remarks
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Q&A

OUR MISSION

Life-transforming therapies

for patients with serious muscle diseases

Driving Toward Meaningful Clinical Data in DM1 & DMD in H2 2023

ACHIEVE | DELIVER

Global, Randomized Placebo-Controlled Trials Designed to Be Registrational

Dosing Patients at Predicted Pharmacologically Active Doses

Significant Unmet Patient Need Provides Confidence in Ability to Enroll Rapidly

ACHIEVE	DELIVER
Safety, Tolerability & Splicing Data Expected in H2 2023	**Safety, Tolerability & Dystrophin Data Expected in H2 2023**

Cash Runway Now Expected to Extend Through 2024

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
- Two clinical-stage programs in DM1 and DMD, advancing FSHD to the clinic
- Clinical data in DM1 and DMD expected in H2 2023

Exceptional Team

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

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Q&A

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)

NO approved therapies

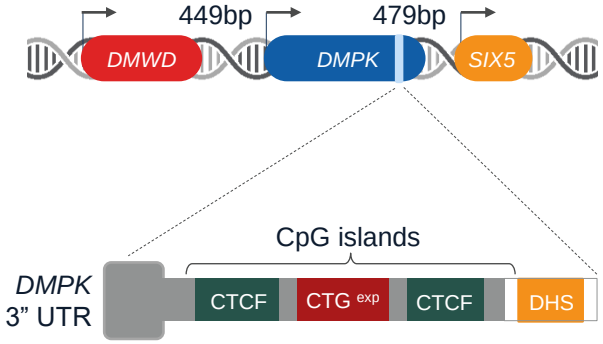
OUR APPROACH

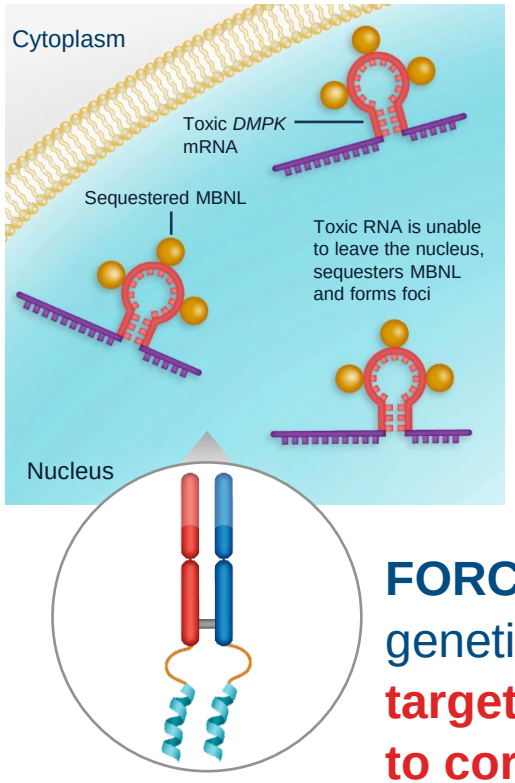
Disease-Modifying Nuclear *DMPK* Knockdown

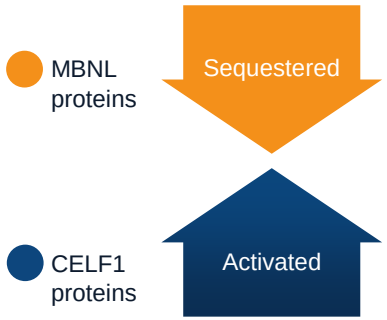
Targeting toxic gain of function *DMPK* RNA to potentially **stop or reverse** disease progression

FORCE Targets the Genetic Basis of DM1 to Correct Splicing

DNA Triplet Repeats → **Toxic RNA Forms Foci in Nucleus** → **RNA Binds Splicing Proteins** → **Clinical Presentation**



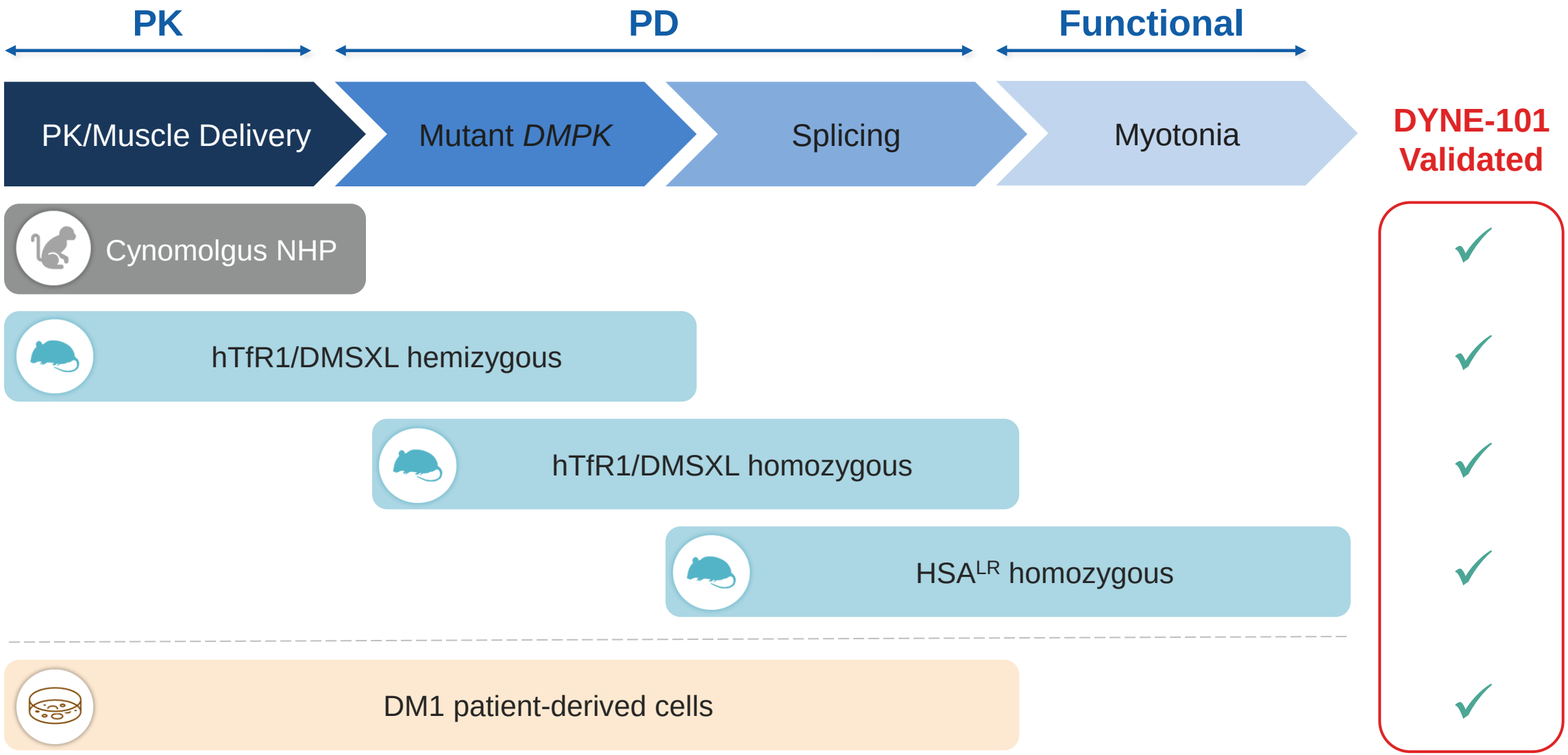




- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

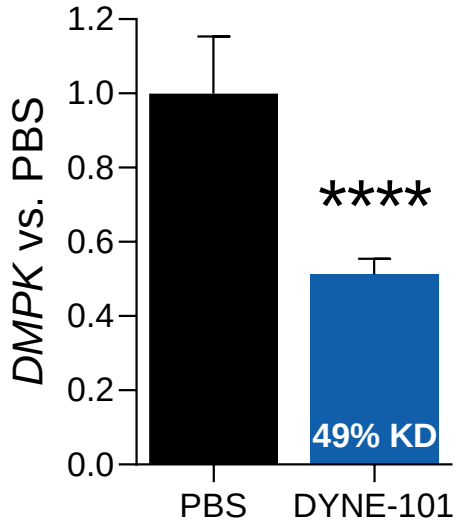
FORCE designed to address the genetic basis of disease by **targeting toxic nuclear *DMPK* RNA to correct spliceopathy**

Robust Preclinical Data Supporting the Potential of DYNE-101 to Drive Disease Modification in the Clinic

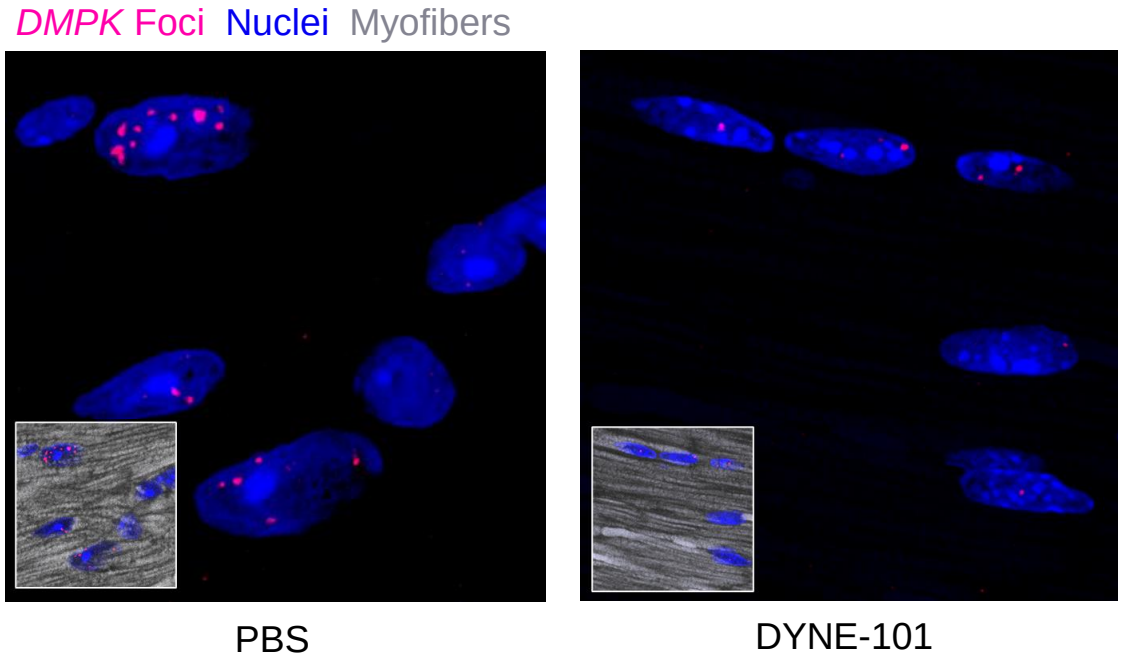


DYNE-101 Demonstrated Toxic *DMPK* KD, Foci Reduction and Splicing Correction in Heart of hTfR1/DMSXL Homozygous Model

Toxic Human *DMPK* RNA KD

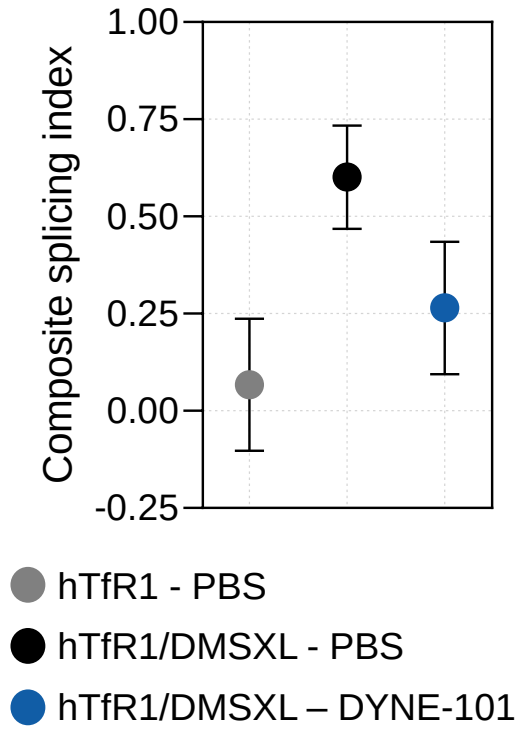


Toxic Human *DMPK* Foci Reduction



DYNE-101 reduces foci area by 49%*

Splicing Correction



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.

DYNE-101 Achieved *DMPK* Knockdown & Well Tolerated in NHPs

Robust WT *DMPK* KD Achieved in Skeletal, Cardiac and Smooth Muscles

- Up to 70% *DMPK* KD at 2 months with low monthly dosing

13-Week GLP Toxicology Study[1]

- No dose limiting toxicity observed up to a maximally feasible dose[2]
- 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

Notes: 1. Based on conclusions of report from third-party CRO. 2. Dosed once every three weeks.
NOAEL: No-observed-adverse-effect level

ACHIEVE Trial Informed by Multiple Stakeholders

Global, Multi-disciplinary KOL & Regulatory Input

- Overall design for the MAD portion in patients ages 18 to 49
- 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

Phase 1/2 Clinical Trial to Evaluate DYNE-101 in Patients with DM1

Population

- Adult patients living with DM1
- Ages 18 to 49 years
- ~64 adult participants

Primary Endpoints

- Safety and tolerability

Key Secondary Endpoints

- Pharmacokinetics
- Change from baseline of:
  - Splicing
  - *DMPK* RNA expression
  - Multiple assessments of muscle strength and function

Stages of ACHIEVE

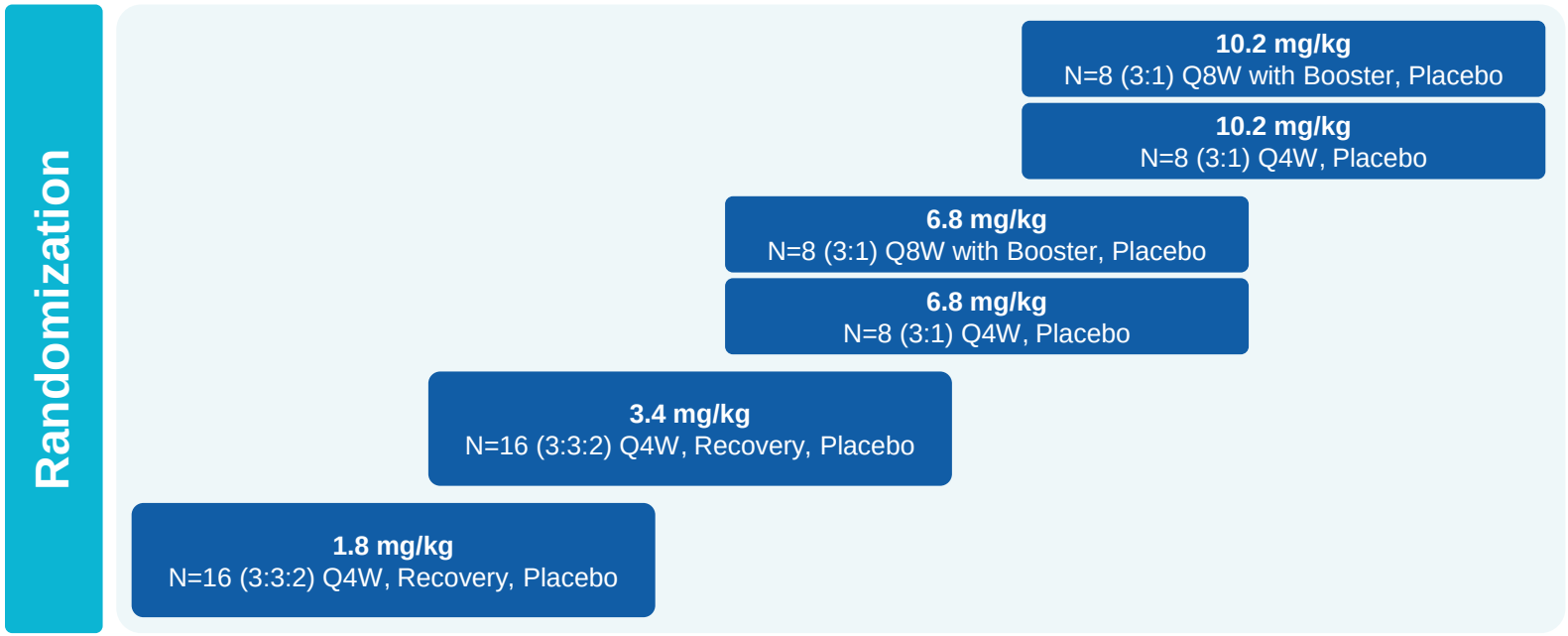
- Multiple Ascending Dose (MAD): 24 weeks
- Open-Label Extension (OLE): 24 weeks
- Long-Term Extension (LTE): 96 weeks

Safety, Tolerability & Splicing Data Expected in H2 2023

Multiple Ascending Dose Stage of ACHIEVE

ACHIEVE

Global, Randomized, Placebo-Controlled Stage Evaluating Once Monthly or Less Frequent Administration of DYNE-101 in ~64 Adult Patients Living with DM1



MAD Study Details

- IV administration of DYNE-101 or placebo every 4 weeks or every 8 weeks
- Muscle biopsies: Baseline, 12 weeks, 24 weeks
- Patients in MAD study escalated to highest tolerable dose in OLE and LTE

Global Strategy & Adaptive Trial Design Enable Rapid Achievement of Potentially Registrational Clinical Data

Doses provided refer to ASO component of DYNE-101. Recovery cohort Q4W x 2 doses then placebo for the remainder of the 24W placebo-controlled period. Q8W with booster includes Q4W x 3 doses then Q8W dosing.

DM1 Community Urgently Needs Treatment Options

“I cannot do certain things now that I could do last year. And, I know, a year from now, there are certain things I will not be able to do. So, anything that would even just stop the progression, or even slow the progression of the disease, would be really invaluable.

And, of course, if there's a way to actually reverse some of the symptoms, that's like the overall dream. And, I think, really just stopping it in it tracks, would be really phenomenal.”

Joachim Boekelmann

Program

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Perspectives on Myotonic Dystrophy Type 1 (DM1)
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Q&A

PERSPECTIVES ON MYOTONIC DYSTROPHY TYPE 1

Valeria A Sansone, MD, PhD
Full Professor of Neurology, University of Milan
Neurorehabilitation Unit
Clinical and Scientific Director of the NEMO Center

Disclosures

I provide intellectual consultation in Advisory Boards/teaching activities for Biogen, Roche, Novartis, Dyne, Lupin, PTC, Santhera, Amylyx

Perspectives on Myotonic Dystrophy Type 1

Overview

- Patient journey
- Unmet needs in DM1
- How is research addressing these?
  - What functional endpoints are most important?
  - What level of splicing matters?
  - What is clinically meaningful?
- How is the clinical development landscape evolving

Prevalence

DM1 is the most frequent muscular dystrophy of adulthood

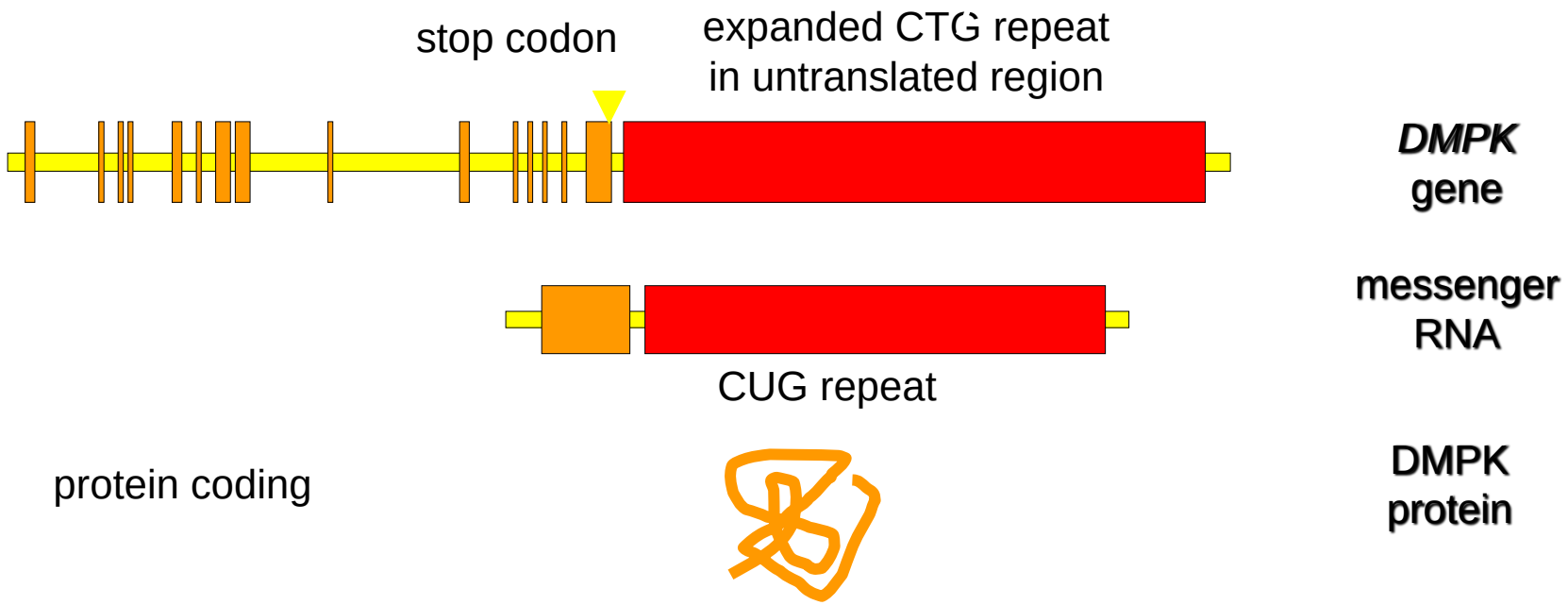
1:~~9~~000

1:3500

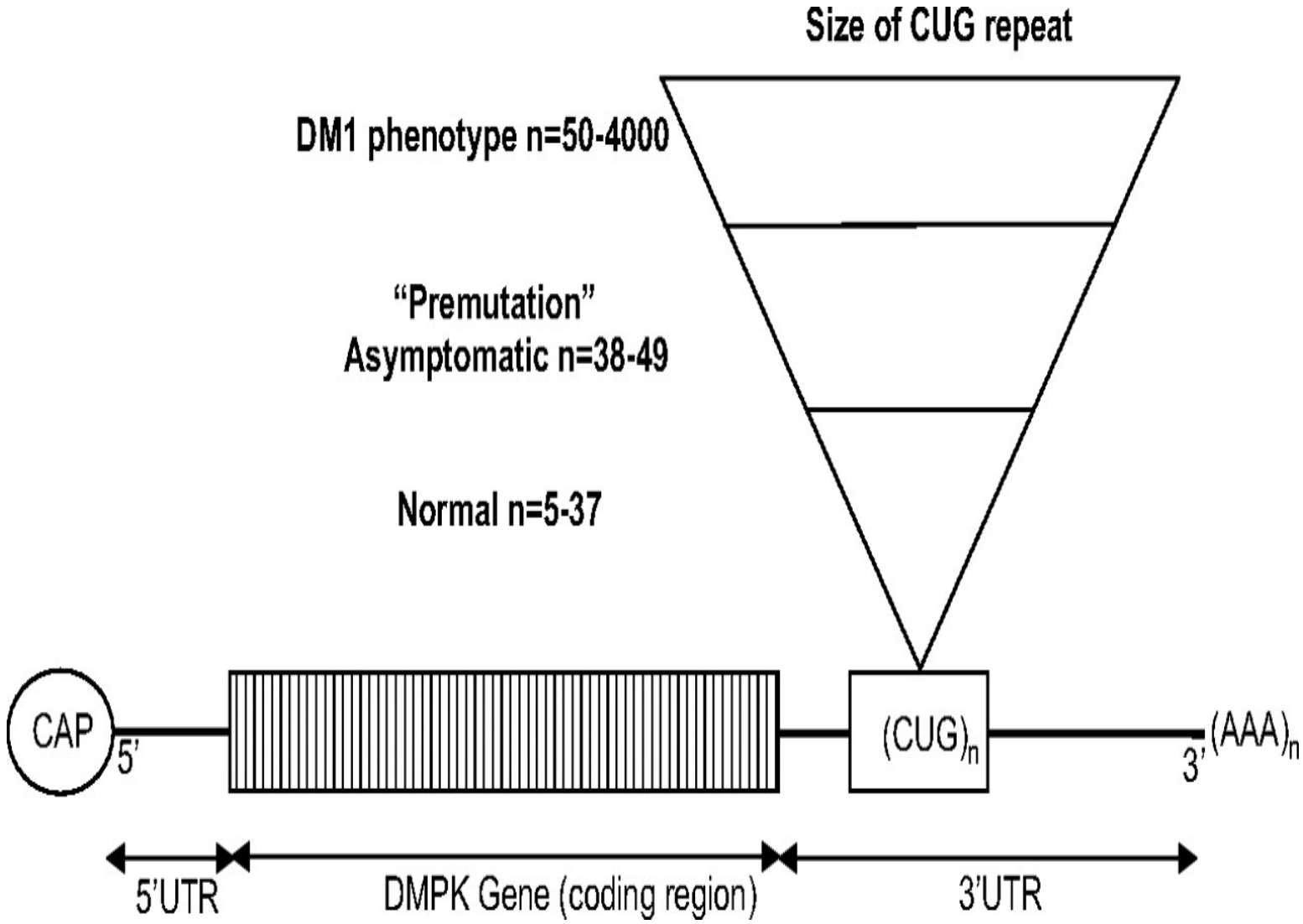
Nicholas Johnson
MDF meeting Philadelphia Sept. 2019

Myotonic dystrophy is an expansion disorder

Gene	DMPK (chr. 19)
Protein	protein kinase
Location	3’ untranslated



CTG expansions



DM1: Onset At All Ages

40 yrs

18 yrs

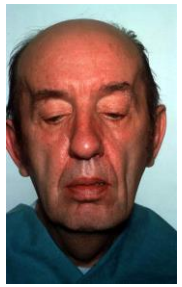
30 days
birth

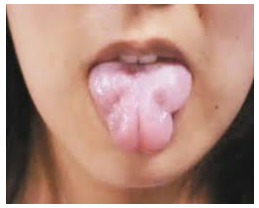
LATE ONSET

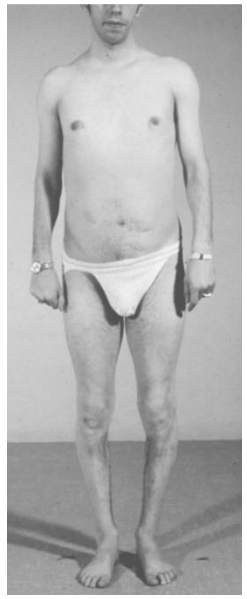
ADULT ONSET

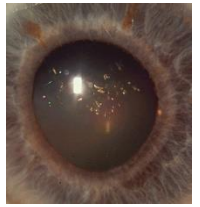
PEDIATRIC ONSET

CONGENITAL FORM





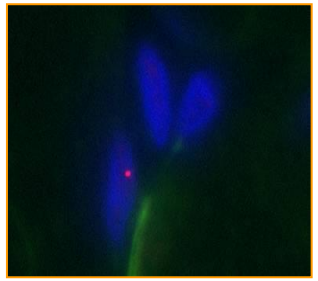




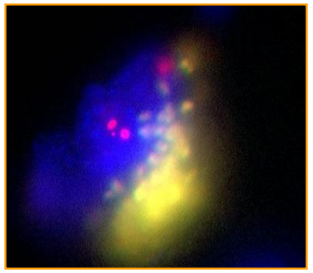
Myotonic Dystrophy is a spliceopathy
RNA-mediated toxic disease

expanded CTG repeat (DNA)

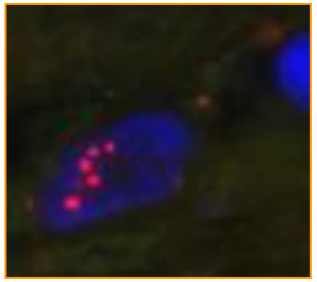
∧ expanded CUG repeat (RNA)



skeletal muscle

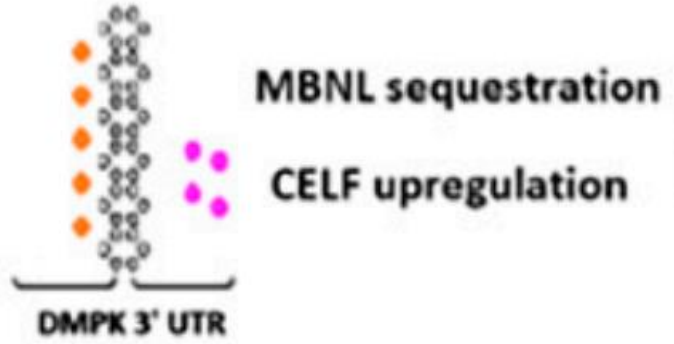


cortical neuron



heart

Kind courtesy of Charles Thornton



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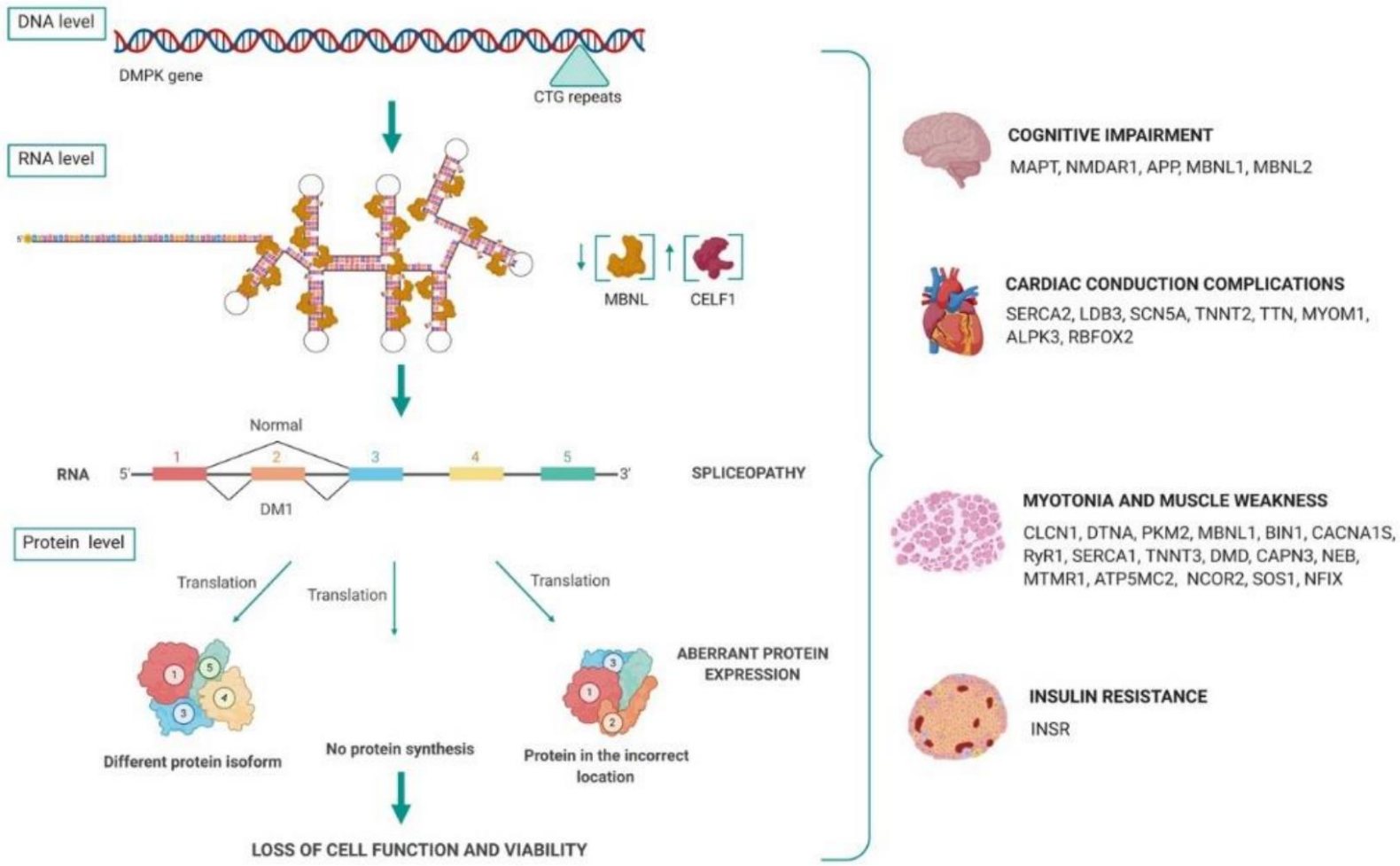


Patient journey

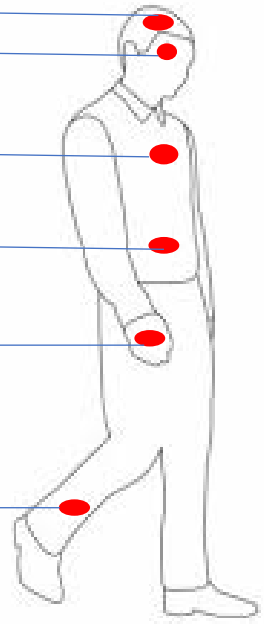
Frontal balding
Initial cataracts

Asymptomatic
AV block

GI problems

Fluctuating myotonia
Warm-up phenomenon

Stepping gait
L5 radiculopathy???



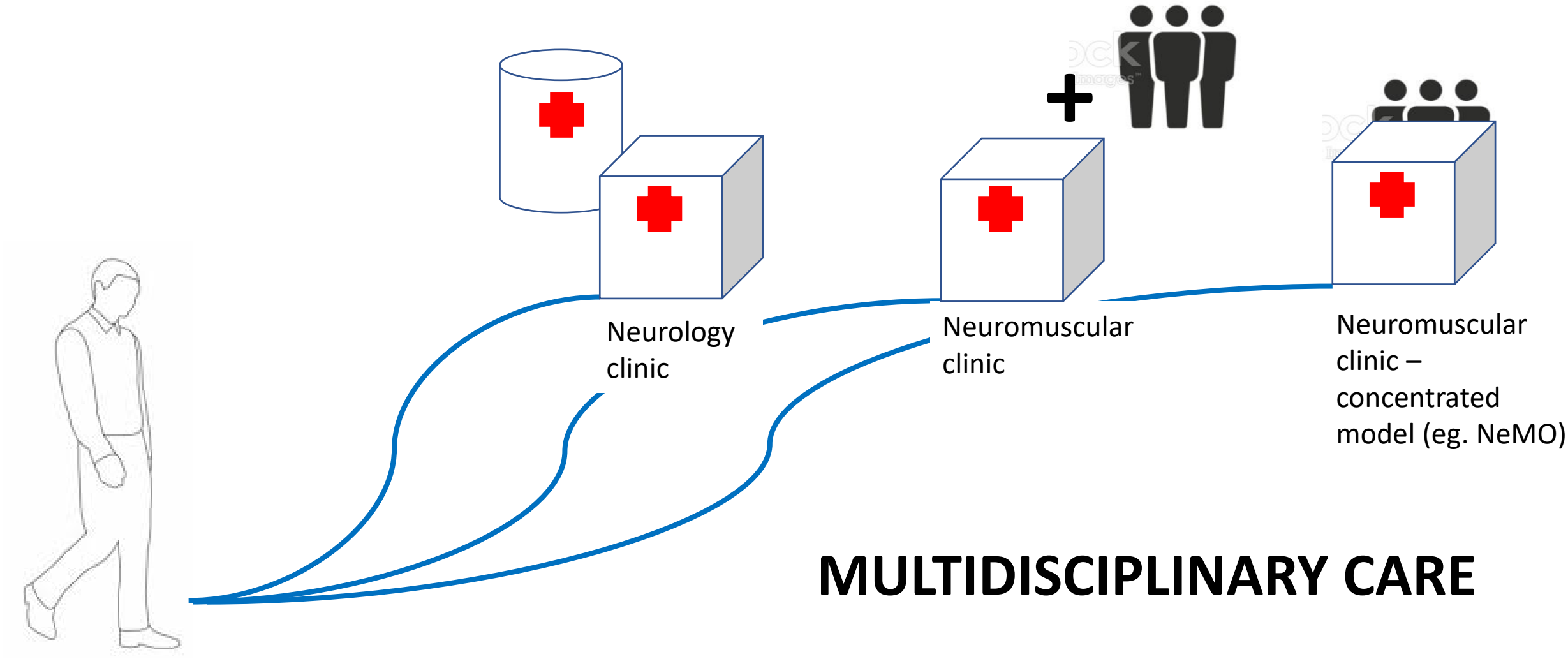
DIAGNOSTIC DELAY!!!

Published in final edited form as:
J Neurol. 2013 October ; 260(10): 2497–2504. doi:10.1007/s00415-013-6993-0.

Diagnostic Odyssey of Patients with Myotonic Dystrophy

James E. Hilbert, MS[a], Tetsuo Ashizawa, MD[b], John W. Day, MD, PhD[c], Elizabeth A. Luebbe, MS[a], William B. Martens[a], Michael P. McDermott, PhD[a,d], Rabi Tawil, MD[a], Charles A. Thornton, MD[a], Richard T. Moxley III, MD[a], and the Registry Scientific Advisory Committee[*]

Patient journey



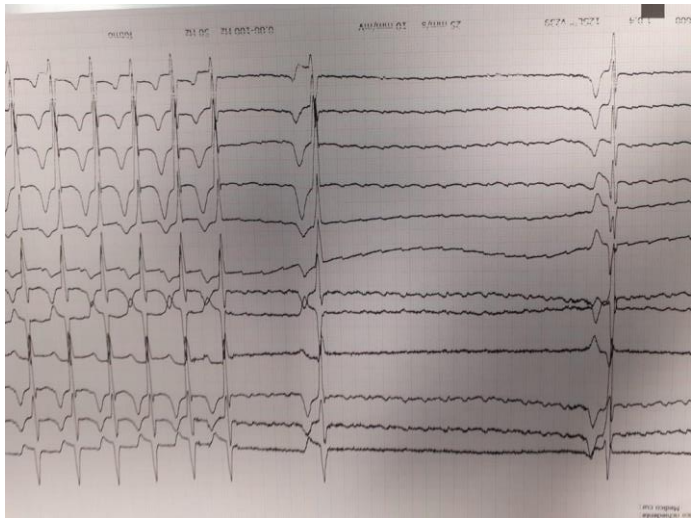
MULTIDISCIPLINARY CARE

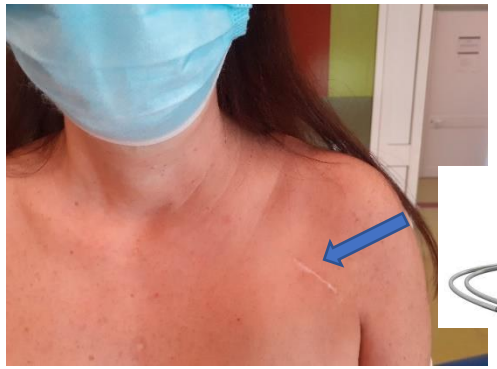
Burden Of Disease

Distal muscle weakness

Stumbles and falls

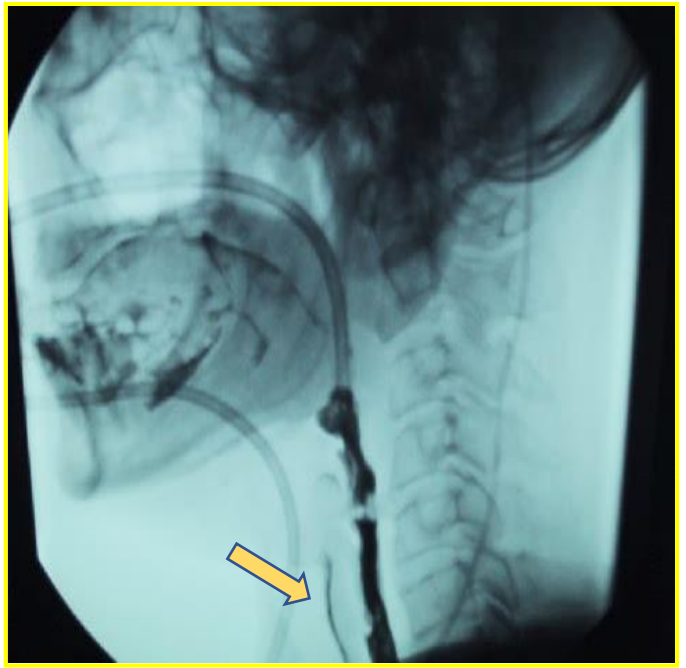
Cardiac arrhythmias





Early PM/ICD implantation

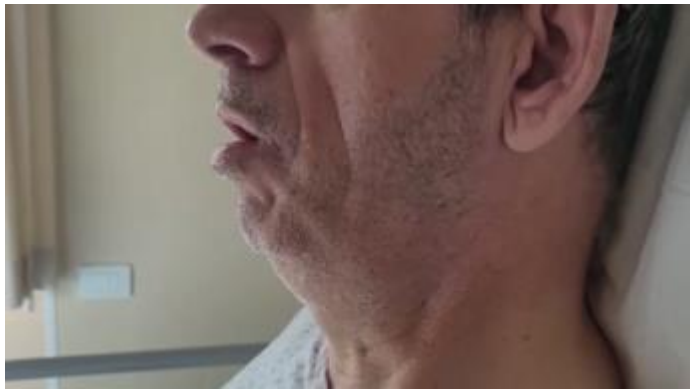
Smooth muscle involvement



Swallowing difficulties
GI symptoms

Burden Of Disease

Respiratory muscle weakness



Secretion management
Daytime hypoxia
Hypercapnia

Cognitive & behavioral abnormalities

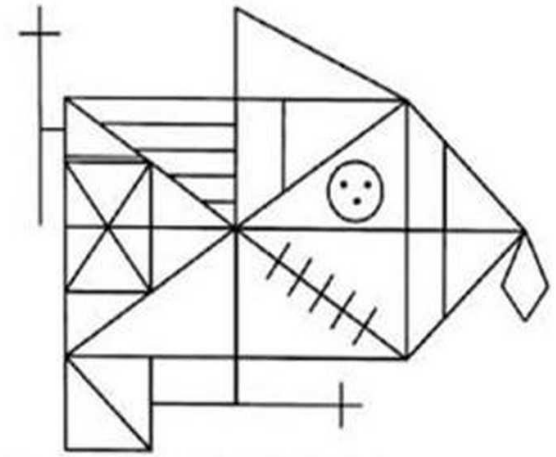
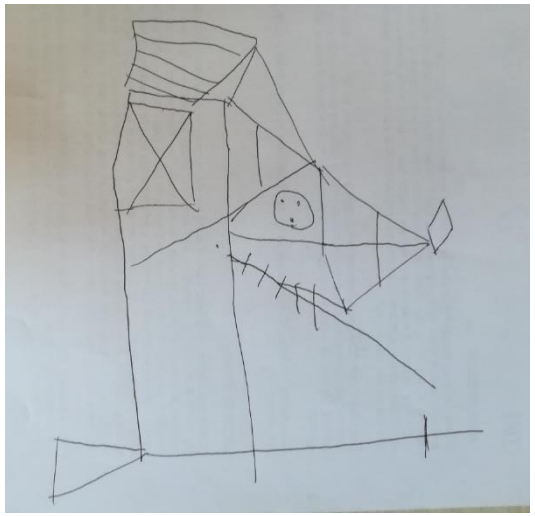


Figura 2. Figura Compleja de Rey-Osterrieth



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

Unmet needs

No Treatment!

Unmet needs

COGNITIVE IMPAIRMENT

MAPT, NMDAR1, APP, MBNL1, MBNL2

→ **EXCESSIVE DAYTIME SLEEPINESS**

SLOWED THINKING

FATIGUE

MYOTONIA AND MUSCLE WEAKNESS

CLCN1, DTNA, PKM2, MBNL1, BIN1, CACNA1S, RyR1, SERCA1, TNNT3, DMD, CAPN3, NEB, MTMR1, ATP5MC2, NCOR2, SOS1, NFIX

↗ **MUSCLE WEAKNESS**

FATIGUABILITY

INSULIN RESISTANCE

INSR

→ **CHRONIC RESPIRATORY INSUFFICIENCY**

↘ **GI PROBLEMS**

Research & Unmet needs

➢ *What functional endpoints are most important?*

COGNITIVE IMPAIRMENT

MAPT, NMDAR1, APP, MBNL1, MBNL2

MYOTONIA AND MUSCLE WEAKNESS

CLCN1, DTNA, PKM2, MBNL1, BIN1, CACNA1S, RyR1, SERCA1, TNNT3, DMD, CAPN3, NEB, MTMR1, ATP5MC2, NCOR2, SOS1, NFIX

EXCESSIVE DAYTIME SLEEPINESS 91% ..... **How?**

Heatwole C et al. Neurology 2012. Patient-reported impact of symptoms in myotonic dystrophy type 1 (PRISM-1)
Sansone VA, Proserpio P, Mauro L, et al. Assessment of self-reported and objective daytime sleepiness in adult-onset myotonic dystrophy type 1. *J Clin Sleep Med*. 2021;17(12):2383–2391

MUSCLE WEAKNESS
FATIGUABILITY

CHRONIC RESPIRATORY INSUFFICIENCY ..... **How? When?**

Carola R. Ferrari Aggradi, Elisa Falcier, [...], and Valeria A. Sansone. Assessment of Respiratory Function and Need for Noninvasive Ventilation in a Cohort of Patients with Myotonic Dystrophy Type 1 Followed at One Single Expert Center. Can Resp J 2022

44% WITH INDICATION FOR NIV; 10% WORSENS OVER 5 YEARS; 25% ADHERENT

GI PROBLEMS 83% ..... **How?**

Research & Unmet needs

➢ **What level of splicing matters?**

20-25% of DMPK RNA knock-down could be relevant

- different proteins are impaired by CTG expansion

- CTG expansion varies in different tissues

The amount of knock-down may have a different impact in different organs and on symptoms

Research & Unmet needs

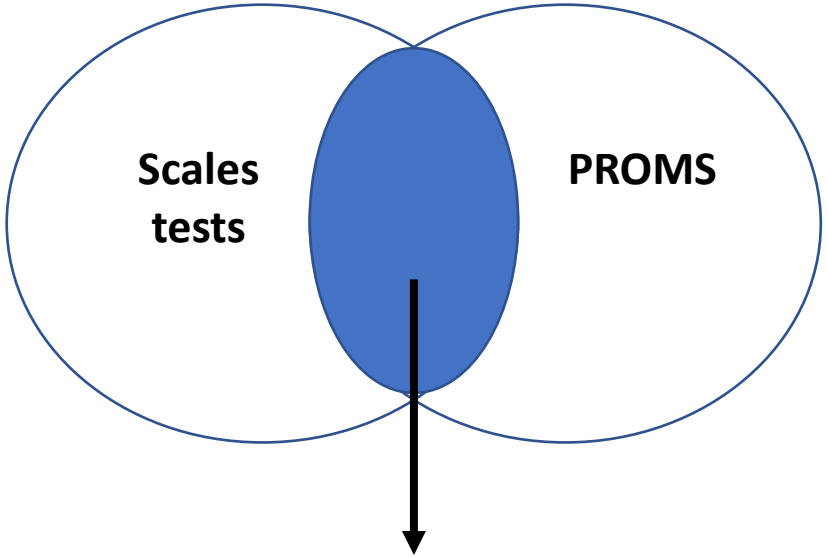
➢ **What is clinically meaningful?**

Weakness
x MRC scale
✓ Function

Fatigue
How?

Sleepiness
How?

GI dysfunction
How?



CLINICALLY MEANINGFUL?
For how long???

PATIENTS ≠ CLINICAL RESEARCHERS ≠ REGULATORS/PAYERS

SMA experience

The FORCE Platform & Unmet needs

- **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

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

WHAT STRENGTHS OF THE FORCE PLATFORM ARE IMPORTANT FOR PATIENTS

- Robust preclinical data
- Consistent findings in vitro, in vivo and NHP
- Target tissues
- Little off-target effects
- Durable effects

Clinical development landscape is changing

Transcriptional silencing

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

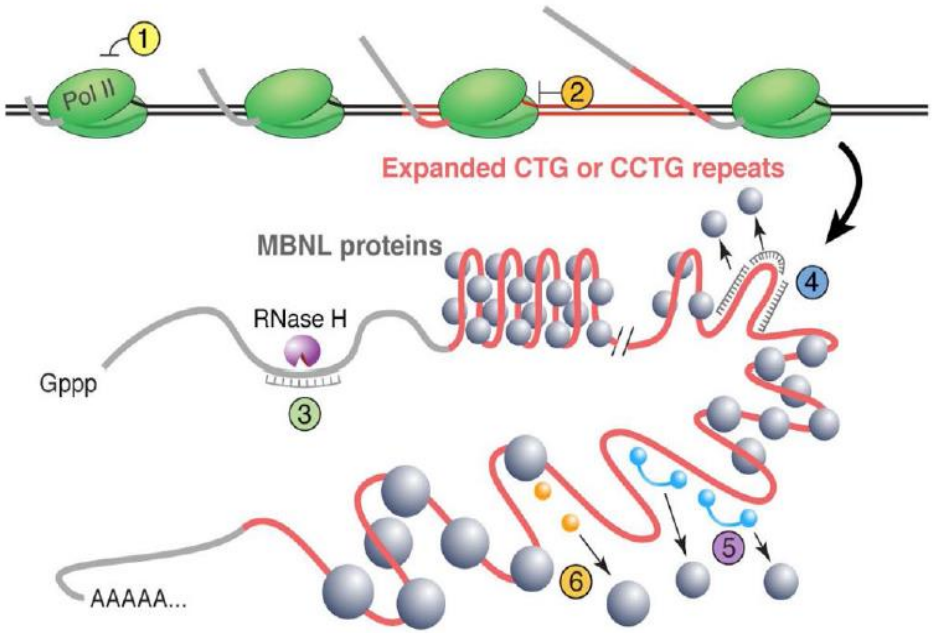
Post-transcriptional silencing

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

SMA experience
- Safety profile
- Durability of action

ASOs | **(EXP)n** | **SMALL MOL**

CLINICAL TRIAL READINESS

Myotonic Dystrophy – Clinical Research Network (DM-CRN)

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

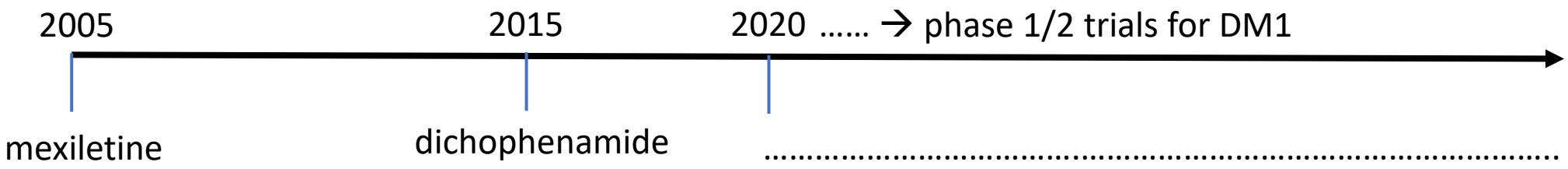
DM-CRTN MEETING
Virgina University
October 24-28 2022

Conclusions

- ✓ PATIENTS are becoming more and more PROACTIVE
- ✓ DM1 experts are seeing patients with a different approach

Would this be a good candidate for the trial?
Would there be a clinically meaningful change?

- ✓ There is more hope for our patients



Program

Opening remarks
Joshua Brumm, President & CEO

DYNE-101 ACHIEVE Trial
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on Myotonic Dystrophy Type 1 (DM1)
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Professor of Neurology, University of Milan

Q&A

Program

DYNE-251 DELIVER Trial
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on Duchenne Muscular Dystrophy (DMD)
Richard Finkel, M.D., Director, Center for Experimental Neurotherapeutics, St. Jude Children's Research Hospital

Q&A

Closing remarks
Joshua Brumm, President & CEO

Building a Global DMD Franchise of Transformative Therapies

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)

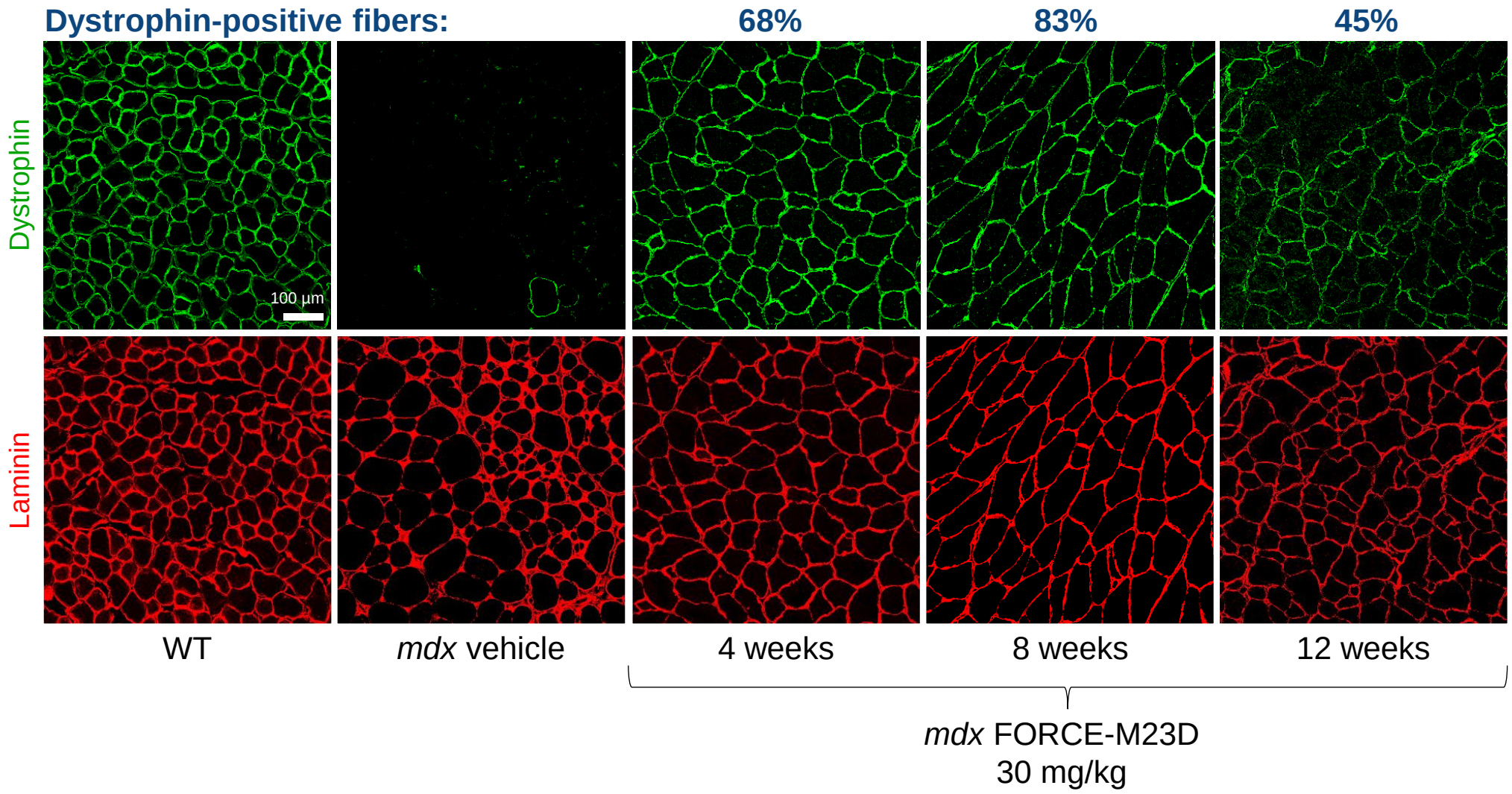
Current Approved Exon 51 Therapies Only Increased Dystrophin Production <1%

OUR APPROACH

Best-in-class Targeted Exon Skipping

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

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.

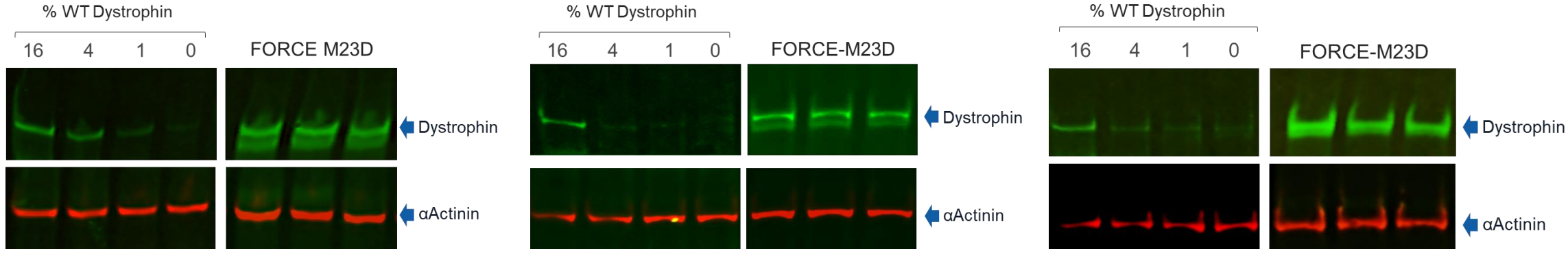
FORCE Achieved Robust and Durable Dystrophin Expression and Sarcolemma Localization in Muscle

Quadriceps

Diaphragm

Heart

Dystrophin expression by WB

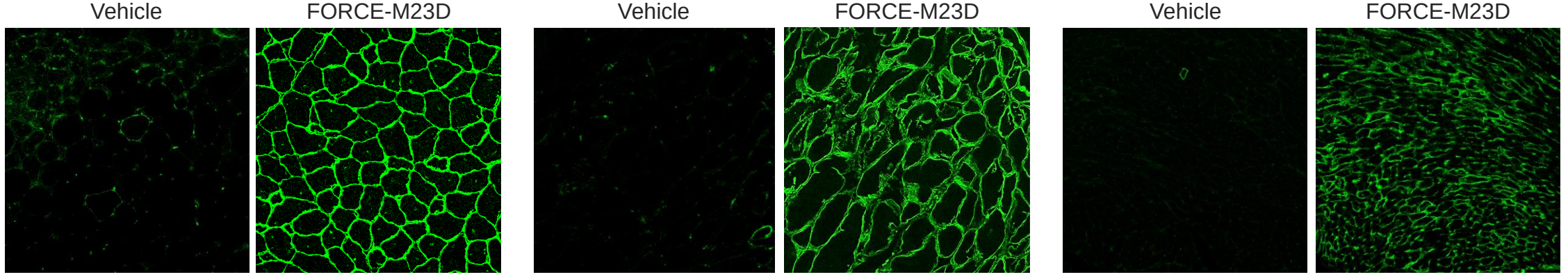


51% of wild-type dystrophin

90% of wild-type dystrophin

77% of wild-type dystrophin

Dystrophin localization to sarcolemma



68% dystrophin-positive fibers

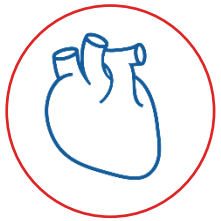
~80% dystrophin-positive fibers

~80% dystrophin-positive fibers

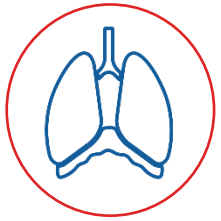
Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0; analysis on week 4 for all muscles. N= 3 - 5 per cohort.

DYNE-251 Demonstrated Robust Exon Skipping & Favorable Safety Profile in NHPs

High Level of Exon 51 Skipping Achieved in Key Muscles at 2 Months[1]



43% in heart



52% in diaphragm

18% in quadriceps

GLP Toxicology Studies: 5-Week & 13-Week[2]

- No dose limiting toxicity observed 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

Notes: 1. Based on 5 weekly doses (Week 0 – Week 4) with tissue analysis at 8 weeks. 2. Based on conclusions of report from third-party CRO.
NOAEL: No-observed-adverse-effect level

DELIVER Trial Informed by Extensive Duchenne Community Engagement

Global, Multi-disciplinary KOL & Regulatory Input

- Overall design for the MAD portion 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

Phase 1/2 Clinical Trial to Evaluate DYNE-251 in Patients with DMD

DELIVER

Population

- Patients with DMD with mutations amenable to exon 51 skipping therapy
- Ages 4 to 16 years
- ~46 male participants
- Ambulant and non-ambulant

Primary Endpoints

- Safety and tolerability
- Change from baseline in dystrophin protein levels by Western Blot

Key Secondary Endpoints

- Pharmacokinetics
- Change from baseline of:
  - Exon 51 skipping levels
  - Muscle tissue PDPF
  - Multiple assessments of muscle function, including NSAA score and certain timed functional tests

Stages of DELIVER

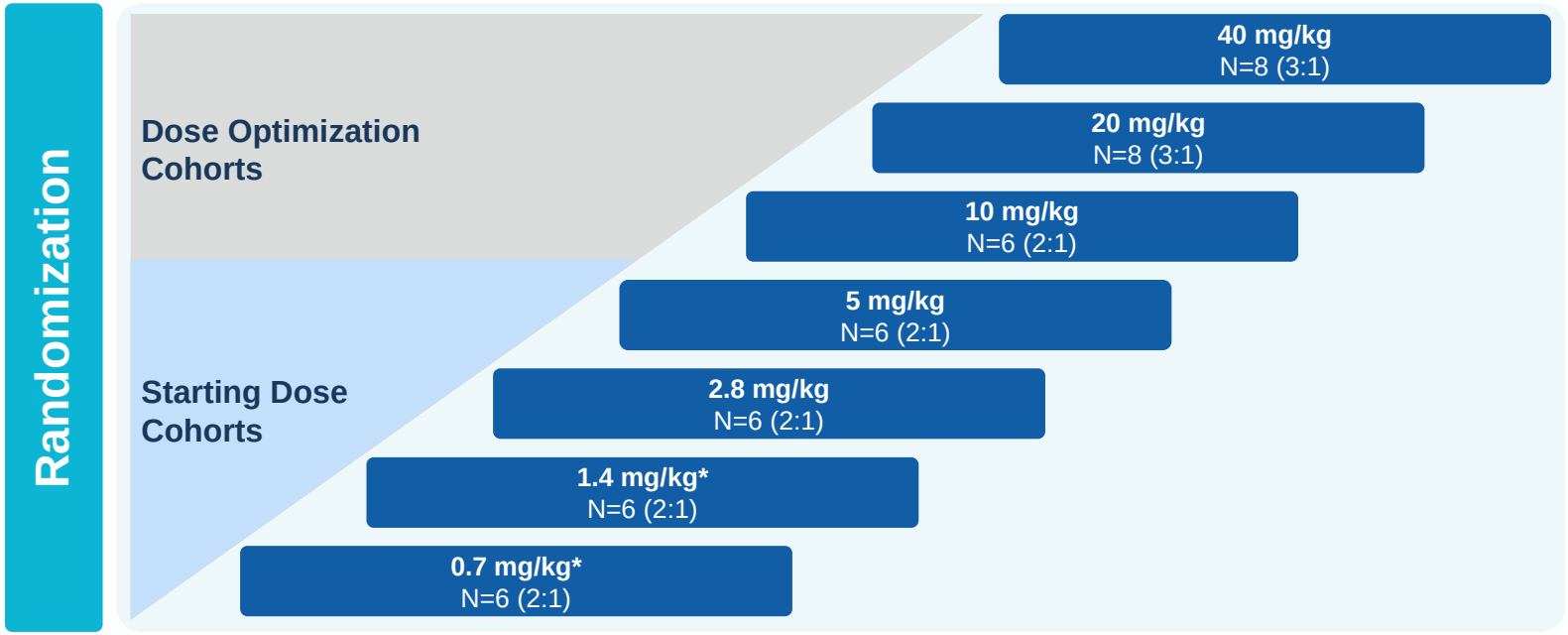
- Multiple Ascending Dose (MAD): 24 weeks
- Open-Label Extension (OLE): 24 weeks
- Long-Term Extension (LTE): 96 weeks

Safety, Tolerability & Dystrophin Data Expected in H2 2023

Multiple Ascending Dose Stage of DELIVER

DELIVER

Global, Randomized, Placebo-Controlled Stage Evaluating Once Monthly Administration of DYNE-251 in ~46 Ambulant and Non-Ambulant Male DMD Patients with Mutations Amenable to Exon 51 Skipping Therapy



MAD Study Details

- IV administration of DYNE-251 or placebo every 4 weeks
- Muscle biopsies: Baseline and 24 weeks in 2.8 mg/kg and higher cohorts
- Patients in MAD study escalated to highest tolerable dose in OLE and LTE

Global Trial Designed to be Registrational and Enable Rapid Achievement of Predicted Pharmacologically Active Dose Levels

Dyne THERAPEUTICS

Patient cohorts will be dosed from 0.7 mg/kg to 40 mg/kg in the U.S. Outside the U.S., starting doses and number of cohorts will vary by region. Doses provided refer to PMO component of DYNE-251. Muscle biopsies taken at baseline and 24 weeks in 2.8 mg/kg and higher cohorts; biopsies not taken in 0.7 mg/kg and 1.4 mg/kg cohorts.

DMD Community Has Urgent Need for Improved Treatment Options

“The treatment options were minimal and they still are minimal. Duchenne muscular dystrophy is a disease that doesn't have a cure.

You know, my biggest fear for Jordan is he might not have the chance to get married or to work or to live out whatever his passions or dreams are. So, a potential transformative treatment for us, is just a hope that he could survive the disease and go on to live a full life.”

Diana Johnson

Program

DYNE-251 DELIVER Trial
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on Duchenne Muscular Dystrophy (DMD)
Richard Finkel, M.D., Director, Center for Experimental Neurotherapeutics, St. Jude Children's Research Hospital

Q&A

Closing remarks
Joshua Brumm, President & CEO

Therapeutic Considerations in Duchenne MD

Richard S. Finkel, MD
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Disclosures – Richard Finkel

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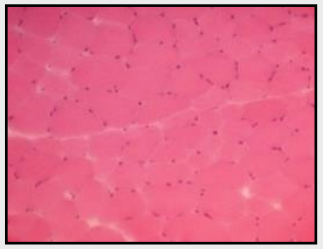
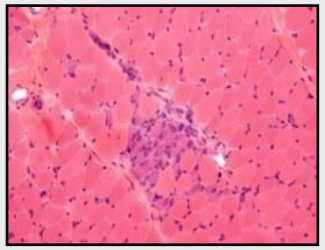
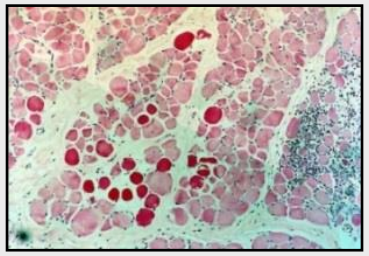
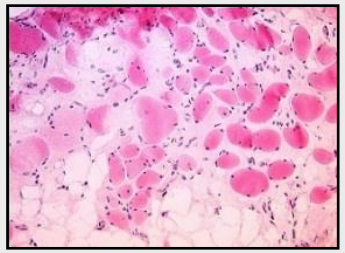
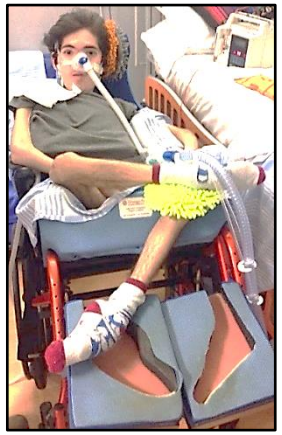
DSMB for Ionis Angelman, Roche Moonfish SMA, Sarepta etiplersen studies

Unpaid participation: EveryLife Foundation, n-Lorem Foundation, MDA, Cure SMA, SMA Europe, Florida and N Carolina State Dept of Health (newborn screening)

Editorial fees from Elsevier

License fees from the Children's Hospital of Philadelphia

The Life Cycle of Duchenne MD

	Newborn/Infant	3-7 years	7 years	Early Teens	Early 20s
Muscle Biopsies					
Clinical Course	 ↑CK, NFkB				

Progressive weakness, respiratory failure, cardiomyopathy and premature death

The Duchenne MD Lifecyle

Birth 2 4 6 8 10 12 16 20 30

[Pre-Sx] [Dx][Progression] [End-Stage] [Death]

Gross Motor Skills:

Normal

Slowly gaining

Plateau phase

Regression in gait

Loss of ambulation

Regression in upper limb function

Scoliosis

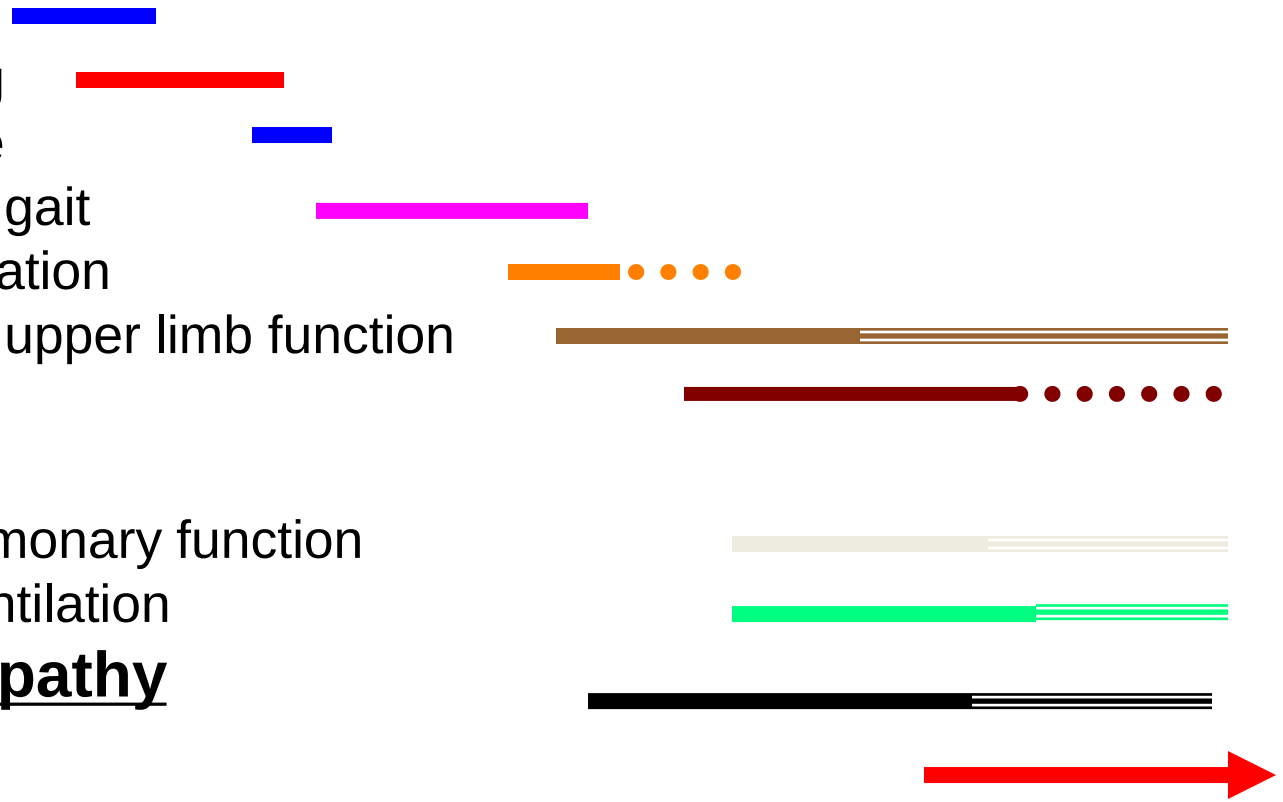
Pulmonary

Decline in pulmonary function

Sleep hypoventilation

Cardiomyopathy

Death



Multi-disciplinary Support Has Impacted the Natural History of DMD

1. **Physical, Occupational and Speech Therapy**
2. **Musculoskeletal: scoliosis, joint contractures**
3. **Pulmonary**
4. **Cardiac (cardioprotective Rx)**
5. **Nutrition**
6. **Psychosocial**

- Neurologist, NP, Clinic RN
- PT, OT, S/LP
- Orthopedics
- Pulmonary
- Cardiology
- Physiatry
- Social Worker
- Genetic Counselor
- Clinic Coordinator
- Data Coordinator

Current & Emerging Treatment Approaches for DMD

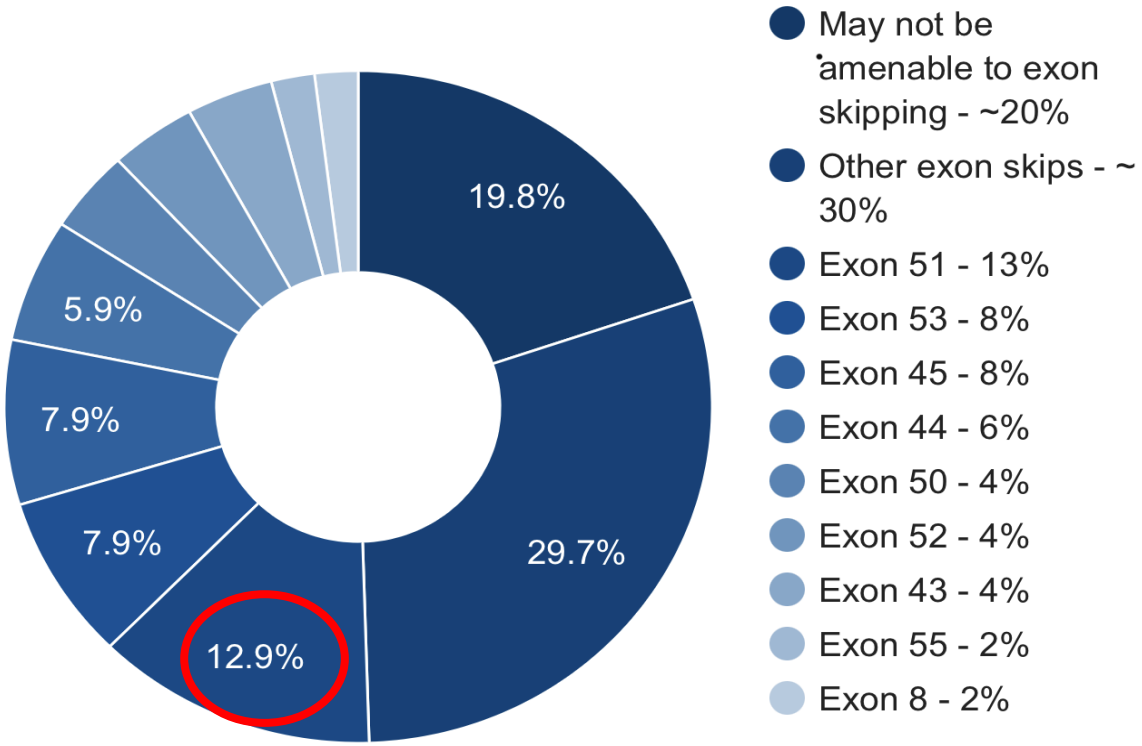
1. Glucocorticoids: prednisone, deflazacort, vamorolone

2. DNA/RNA directed therapies to increase dystrophin
   A. Readthrough of premature stop codons: ataluren
   B. Exon Skipping:
      - PMOs: 4 currently FDA approved (IV, weekly)
      - Cell-penetrating peptide PMO conjugate
      - Antibody PMO conjugate
   C. AAV/exon skipping: U7snRNA skipping of exon 2
   D. Gene replacement therapy
   E. CRISPR/Cas9 gene editing

3. Dystrophin independent
   A. Utrophin upregulation
   B. Myostatin inhibition, follistatin
   C. Anti-inflammatories

Exon skippable deletions ~80% of Duchenne

Skippable DMD mutations



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

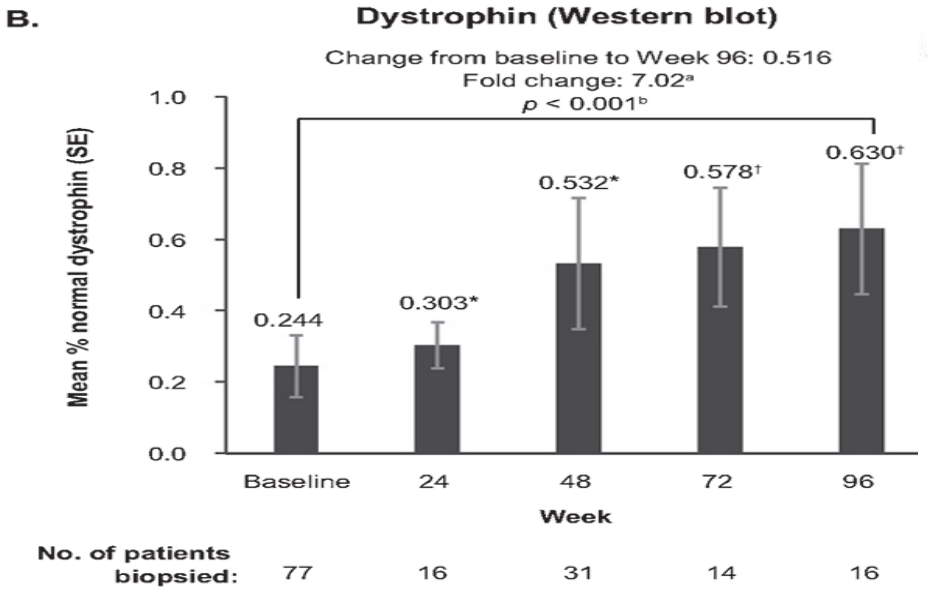
Current Therapy for Exon 51 Skip-Amenable Mutations Demonstrates Limited Dystrophin Increase

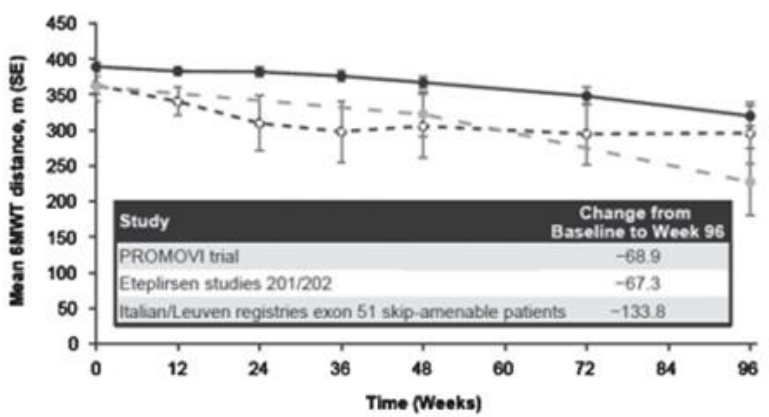
Analyses of dystrophin:

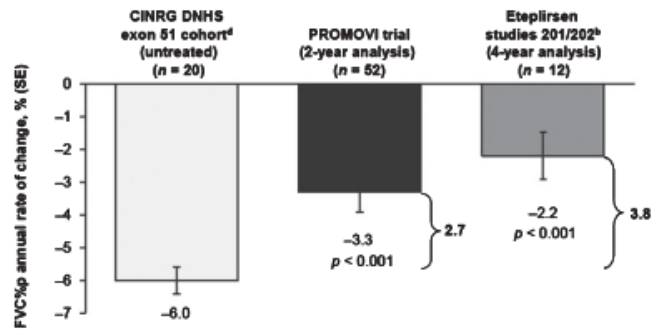
Eteplirsen 30mg/kg, Q1W Dosing Dystrophin at Week 24	Eteplirsen 30mg/kg, Q1W Dosing Change in Dystrophin at Week 96
0.303 % normal dystrophin	0.516 % normal dystrophin

Post-hoc analyses of function:

Measure	Eteplirsen 30mg/kg, Q1W Dosing Change at Week 96	Natural History Change over 96 Weeks
6MWT, m	-68.9	-133.8
FVC, %p	-3.3	-6.0







McDonald et al Journal of Neuromuscular Diseases 8 (2021) 989–1001 DOI 10.3233/JND-210643

ASOs for Treatment of Muscular Dystrophy

1. Exon skipping is a proven mechanism to address the genetic basis of disease

2. 2'-MOEs and unconjugated PMOs do not get into muscle very well, which limits dystrophin production and functional benefit

3. Key considerations for therapies in development
   A. How can ASO penetration to skeletal (including diaphragm) and heart be enhanced?
   B. How well is the therapeutic agent retained in muscle – PD effect, sustained steady state, frequency of dosing?
   C. How well are muscle fibers transduced?
   D. What is the safety / toxicity profile? Is there a wide safety margin?

Why the need for a next-gen ASO for DMD?

DYNE-251

1. Chemistry
   - Fab: Antigen binding fragment, targets the transferrin receptor 1 in skeletal and cardiac muscle
   - Clinically validated linker
   - Phosphorodiamidate morpholino oligomer (PMO)

2. Potential advantages as compared to currently approved exon 51 skipping ASO
   - Better target engagement in skeletal and cardiac muscle
   - Strong preclinical data supporting entry into the clinic
   - Less frequent dosing to decrease patient burden
   - Sustained PD effect
   - Favorable safety profile
   - Prospect for more impactful clinical response

Consider different responses along the life cycle of DMD

Infant with minimal dystrophic changes (newborn screening is critical)

Ambulant child

Non-ambulant Adolescent with more advanced dystrophic changes

Adult with advanced skeletal, evolving cardiac and pulmonary disease

Consider different responses along the life cycle of DMD

Infant with minimal dystrophic changes

Ambulant child

Non-ambulant Adolescent with more advanced dystrophic changes

Adult with advanced skeletal, evolving cardiac and pulmonary disease

Skeletal muscle

Motor function >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Consider different responses along the life cycle of DMD

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Non-ambulant Adolescent with more advanced dystrophic changes
Adult with advanced skeletal, evolving cardiac and pulmonary disease

Skeletal muscle

Motor function >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Breathing>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Consider different responses along the life cycle of DMD

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Skeletal muscle

Motor function >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Breathing>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Cardiac muscle

Consider different responses along the life cycle of DMD

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Ambulant child
Non-ambulant Adolescent with more advanced dystrophic changes
Adult with advanced skeletal, evolving cardiac and pulmonary disease

Skeletal muscle

Motor function >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Breathing>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Cardiac muscle

Heart failure>>>>>>>>>>>>>>>>>>>>>>

St. Jude Children's Research Hospital

Consider different responses along the life cycle of DMD

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Adult with advanced skeletal, evolving cardiac and pulmonary disease

Skeletal muscle

Motor function >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Breathing>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Cardiac muscle

Heart failure>>>>>>>>>>>>>>>>>>

Arrhythmia>>>>>>>>>>>>>>

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Robust Portfolio Focused on Muscle Diseases

DISEASE	TARGET	DISCOVERY / PRECLINICAL / PHASE 1/2	ESTIMATED PATIENTS
Myotonic Dystrophy Type 1 (DM1)	DMPK	**DYNE-101** — *Safety, Tolerability & Splicing Data Expected in H2'23*	US: **>40,000** Europe: **>74,000**
Duchenne Muscular Dystrophy (DMD)	Exon 51	**DYNE-251** — *Safety, Tolerability & Dystrophin Data Expected in H2'23*	US: **~12,000-15,000** Europe: **~25,000**
	Exon 53		
	Exon 45		
	Exon 44		
	Other Exons		
Facioscapulohumeral Muscular Dystrophy (FSHD)	DUX4	**DYNE-301**	US: **~16,000-38,000** Europe: **~35,000**

Pipeline Expansion Opportunities

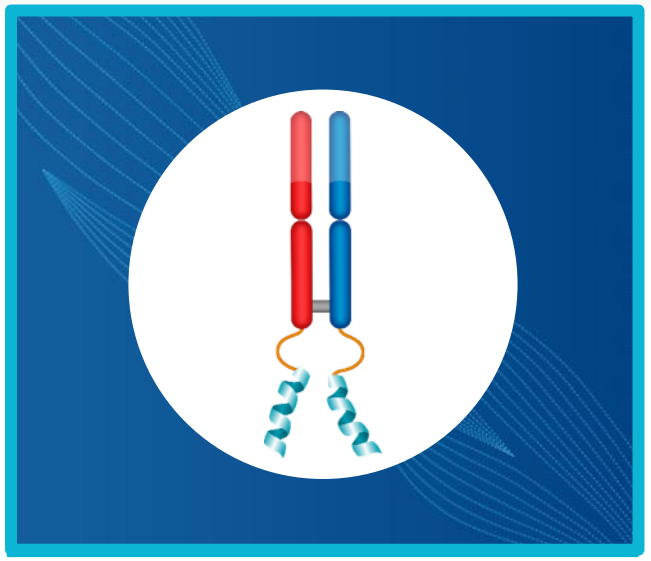
Rare Skeletal

Cardiac

Metabolic

Building the World's Leading Muscle Disease Company

Win in DM1, DMD, FSHD



Own Muscle Delivery

Dynamo Culture